DEC 1 1 1931

AMERICAN JOURNAL of PHARMACY

SINCE 1825

A Record of the Progress of Pharmacy and the Allied Sciences

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Vol. 103 — **NOVEMBER, 1931** — **No. 11**

CONTENTS

Editorials:

"American Medicine" Speaks 621

The Druggist's Place in First Aid 625

Original Articles:

A Pharmacognostical Study of Derris. (Illustrated.) By Heber W. Youngken, Boston, Mass. 628

Tincture of Ferric Chloride. By Arthur Osol, Philadelphia, Pa. 638

A Note on the Comparison of the Physiological Activity of Fluid Extracts of Ergot as Determined by the Cock's Comb and Colorimetric Methods. By Tillman B. Gerlough, New Brunswick, N. J. 644

The Story of Alcohol. By C. Clifton Pines, Philadelphia, Pa. 648

Abstracted and Reprinted Article:

The Medical Aspect of Protein Disturbances. (Reprinted From the *Journal of Chemical Education*) 657

Medical and Pharmaceutical Notes 673

News Items and Personal Notes 681

Price $3.00 per Annum in Advance — **Foreign Postage, 25 Cents Extra**

Single Numbers, 30 Cents. Back Numbers, 50 Cents

Entered as Second-Class Matter at the Post Office at Philadelphia, Pa., Under the Act of March 3, 1879

Acceptance for Mailing at Special Rate of Postage Provided for in Section 1103, Act of October 3, 1917. Authorized February 15, 1930

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THE AMERICAN
JOURNAL OF PHARMACY

VOL. 103 NOVEMBER, 1931 NO. 11

EDITORIAL

"AMERICAN MEDICINE" SPEAKS

EDITORS have at least eleven prerogatives. One of them is the liberal use of the pronoun *We* instead of its bolder form *I*. The other ten comprise an assortment of privileges which when summarized amount to a *carte-blanche* whereby and wherewith an editor can write with the pose of an indisputable authority upon any subject he may elect to discuss, no matter how little he knows about it.

Fortunately, few editors and editorials are taken seriously by discriminate readers for no longer are such persons moved by the magic of a facile pen.

But once in a great while an editorial comes which does prove, at least a "readability," to say nothing however of accuracy and authority.

And proof of these qualities may be had in the reactions which it engenders.

Such an editorial has appeared recently in *American Medicine* (October, 1931) and comments upon it, in pharmaceutical circles, have been none too sweet.

WE reprint it herewith, and invite readers of this Journal to peruse it and to send us their reactions to it.

WE think that it exercises, and fairly strenuously, all the editorial prerogatives aforementioned and possibly a few others, yet it does arrive at certain truths—and it does point to an eventual change in the practice of pharmacy which will certainly segregate the profes-

sional from the commercial type of establishment—and this in the interest of service.

But its depiction of "rampant" substitution is assuredly wrong and unfair. Its delineation of "every up-to-date practitioner"—is totally too complimentary—unless the joker is in the *up-to-date.*

One out of seven—seems to be the ratio established for competent pharmacists, and though the comparison is not quite fair, I am certain that I would not consider ONE out of TEN of the average run of physicians as competent to extricate and extirpate my appendix did it need such treatment.

The paternalistic temerity wherewith the editorial suggests "official dispensaries" is rather typical of certain medical writers—who love paternalism when applied to any calling or profession outside the field of medicine.

But here is the reprint and it "speaks for itself."

THE DRUGGIST, BUSINESS MAN OR PROFESSIONAL MAN

"Time was when the druggist was definitely a professional man—when the neighbors came to him for friendly advice. He applied his knowledge of pharmacy primarily and stocks on his shelves reflected his professional judgment and recognition of patient's needs just as much as a catering to public demand.

"Now it seems all this has changed. True, in smaller towns one will still find occasionally such an old-fashioned drug store. Also in the great cities of the country there are here and there a few prescription druggists who do not consider the sale of books, tinware and food their principal mission in life. But they are few and far between. Today it seems that the drug store is essentially a business venture, in a way a general merchandising proposition. The druggist lays in stocks and lines purely of what he thinks he can sell. There can be no objection to this policy in such varied items as handkerchiefs, toy dogs, fruit juice squeezers, books, coffee urns, cocktail shakers, and the like provided we accept the drug store as being the logical place to buy them.

"It is, however, a far more serious matter when we examine the stocks of drugs and curative agents which give the druggist his name and which are from the viewpoint of public health and welfare a

thousand times more important than his own personal profits from other lines may be.

"We do not wish to accuse the druggist as a man. But we do impugn the system. We have frequently found the Ph.G. in charge of a chain drug store willing to help, regretting that he could not produce some required drug and offering to get it on two or three days' notice. The suspicion arises, however, that the willingness may have been due to the person requiring the drug. We know of many cases where patients with no knowledge of medicine were sold other things than those prescribed or recommended and this doubtless was considered honest merchandising. Many of the men doing this would have been aghast at the thought of substitution in prescriptions. Yet even this evil is widespread as we all know.

"Druggists have said to us: 'We could not live on a prescription business. If we were to stock every proprietary remedy prescribed at some time or another our capital would be swallowed up in no time, turnover would be so slow that many items might deteriorate.' This may be true. We grant that in non-essentials a reasonable selection is all that can be expected. But has the druggist the right not to stock an agent that may be required in an emergency and for which the need, if it arises, is immediate and acute, purely because there is no general call for this item? Here is an example: A hemostatic was required. Quite obviously an offer to secure a hemostatic in three days is childish. Yet in a section of New York that is populous, well-to-do, six out of seven drug stores visited were unable to furnish any hemostatic of the type needed. In fact, five of them had never heard of four proprietary preparations of this type, the names of which would undoubtedly be familiar to *every up-to-date practitioner*. The seventh druggist was a man of discernment and kindliness. He did not have the item desired but knew where he could obtain it, some forty blocks away. He sent his own boy for it and delivered it to the patient's house, a transaction on which he could certainly have made no profit.

"We ask earnestly is this system right? Is it just? Do not present conditions call for a change in the retail drug business either along the lines practiced in Germany, where there are strict licensing requirements and restriction of the number of pharmacies allowed, or along the lines of separating the professional from the commercial things,

perhaps by the establishment of official dispensaries? In the meantime, with substitution of one form or another rampant, with inability to supply emergency needs, with a seeming lack of interest in the professional angle of the druggist business, is it to be wondered at if physicians dispense?"

IVOR GRIFFITH.

THE DRUGGIST'S PLACE IN FIRST AID

In other days, when a man was injured on the street, officious bystanders carried him into the nearest drug store and dumped him on the floor, saying, "Here he is, Doc. Fix him up." The druggist administered restoratives and applied bandages. A crowd gathered, messed up the store, stopped business and pilfered goods from the counter. The druggist received no pay and an unpleasant notoriety.

Such an incident is entirely out of place in modern life. The wise druggist should sternly refuse to take any part in the care of an injured person brought into his store, and may be warranted in locking his doors against the crowd. It is entirely out of place to depict the druggist in the role of the "Good Samaritan." It is not his province to pour balm into the wounds or to bind them up. The ill or injured should be carried to the hospital, the clinic or the doctor's office. The drug store is not a repair shop for either motor cars, chauffeurs or passengers.

The druggist who allows himself or his assistants to apply first-aid measures exposes himself to the strictures of the medical profession. Whatever he may do will be criticized. In personally applying first aid to the ill and injured the druggist makes himself legally liable for the outcome. In the eyes of the law he is considered as assuming the role of a physician. In some states authorities have notified druggists that in applying first aid they are practicing medicine without a license.

A number of cases have arisen wherein action was brought against druggists for claimed damages resulting from first-aid treatment. Such cases include infection and irritation following the application of a styptic to a bleeding wound; untoward results in a broken limb; claimed injury to the eye in a removal of a cinder. Unscrupulous lawyers are always on the alert, ready to sue the druggist even for his well-intended acts.

In the "Basis Material for a Pharmaceutical Curriculum," issued under the Commonwealth Fund Auspices, the druggist is placed in a wrong position when it is recommended that he should be ready to apply first-aid measures. The Surgeon General of the United States Public Health Service made a similar error in urging druggists to be prepared to apply first-aid treatment. Colleges of pharmacy go astray when they teach students how to practice first-aid measures. To

the "don'ts" named in the charter report, there should be added one for the druggist:

"Don't touch the patient. Send him to a hospital or a physician."

The practice of applying emergency measures to the injured within the walls of a drug store is "loaded."

The druggist, however, has a legitimate place in first aid—an all-important place. The druggist's true place in first aid is educational. He is well within his rights (in fact, he is performing his duty) when he teaches his patrons the necessity for first-aid measures and supplies them with the proper material to carry them out.

It is on record that more than two million accidents occur annually on the highways. Fully as many occur in the homes of our people. To this may be added a million or so of accidents which take place in shops and factories. Here is an enormous toll in the loss of life and limb—a train of suffering, sickness and death.

Much of the disastrous consequences of these injuries could be avoided by the timely application of first aid. We have learned that the slightest injury, even a scratch, pin prick, cut or jam, must be promptly cared for or infection may follow. Industries have established systems for the prompt care of injured employees. They have estimated that an injury not cared for costs in loss of wages compensation an average of over four hundred dollars per case. The saving which would result from an immediate application of first aid in accidents would go a long way toward paying the national debt.

The druggist, above all others, is fitted to spread a knowledge of first aid. He should become a teacher and a preacher—a voice crying out to all mankind, "Protect yourself and help your neighbor." Teaching and preaching first aid creates a want for first-aid material. Every convert becomes a buyer of supplies. An endless chain is formed that ties into the drug store.

There are many avenues through which first aid can be taught. Books are now sold in the drug store. Why not push first-aid manuals and books devoted to home emergencies? These are more profitable than novels. Through them the reader is sent to the drug store to buy the articles named in the volume. The druggist can tie himself up with Boy Scouts, Girl Scouts, women's clubs, parent teachers and athletic associations, and automobile clubs. Lectures and demonstrations can be given. A first-aid class at times holds more fun than a football game, as the boys and girls like to tie themselves up and play

being hurt. Through the Kiwanis, Lions and other clubs, and over the radio, the public can be reached.

Education is the foundation of salesmanship. Every automobilist who enters the store is a prospective buyer for an auto kit. Every householder needs a cabinet containing emergency supplies. Every worker, from the office man to the laborer, should be taught to "be prepared" against the disastrous result of neglected injuries. The traveler and the vacationist, and the man on the street, are first-aid prospects.

An axiom of modern life is the "prevention of infection" following wounds.

The field for first aid lies wide open, waiting for the druggist to come in and occupy the land.

FRED B. KILMER.

ORIGINAL ARTICLES

A PHARMACOGNOSTICAL STUDY OF DERRIS*

By Heber W. Youngken

DERRIS or Tuba Root is being imported in large amounts as an insecticide, and while considerable work is being carried out on the chemistry and insecticidal properties of its active principles and preparations, its pharmacognosy appears to have been neglected.

The materials for this investigation comprised several Gray Herbarium specimens of *Derris elliptica* representing stems, leaf and flowering and leaf and fruiting branches gathered from shrubs growing in the Philippines and Sumatra and respectively collected by E. D. Merrill, A. D. E. Elmer, H. O. Forbes, R. S. Williams and R. M. Holman, about two pound lots of authentic rhizome and root materials of *Derris elliptica* and *Derris malaccensis* obtained from plants growing in the British Experimental Plantation at Serdang, Federated Malay States and very kindly furnished the author by Dr. Smith of the Insecticide Division of the Bureau of Chemistry and Soils, U. S. Department of Agriculture and two commercial lots consisting of rhizomes and roots labeled "Tuba Root," one of which came from Malaya.

It was ascertained through comparative macroscopical and microscopical studies of the authentic materials and the commercial samples of Tuba Root that the latter were derived from *Derris elliptica*. The species known to yield the commercial drug and insecticide are *Derris elliptica* (Roxb.) Bentham, and *Derris malaccensis* Prain, both of which are indigenous to Malaya and parts of the East Indies and members of the *Leguminosæ*.

Description of Derris Elliptica

Derris elliptica (Roxburg) Bentham, known to natives of the Malay Archipelago as "Aker-tuba" and "Tuba Puteh," is a large climbing shrub with purplish-brown stems (longitudinally wrinkled in herbarium material) having scattered circular to elliptical lenticels

*Presented at Annual Meeting of Plant Science Seminar, Gainesville, Fla., July 30, 1931.

and black, closely warted branches. Its leaves are alternate, grayish-green, imparipinnate, up to 15 inches long with 9 to 13 leaflets. The leaflets are oblong, oblong-lanceolate, ob-lanceolate, slightly hairy to glabrous on the upper surface; rusty-tomentose on the lower surface, cuspidate to mucronate at apex, cuneate at base, with entire margin, short petiolate, pinnate-reticulate in venation, the veins of the first order being paired below and alternate toward the summit, the midrib and veins being most prominent on the lower surface, the petiolule rusty-pubescent. The flowers are papilionaceous and occur in axillary compound racemes, the rachis of which exhibits distinct nodes from which pedicels arise, each of the pedicels producing from one to three secondary pedicels, the latter ending with a flower. Each flower consists of a campanulate calyx, a papilionaceous corolla hav-

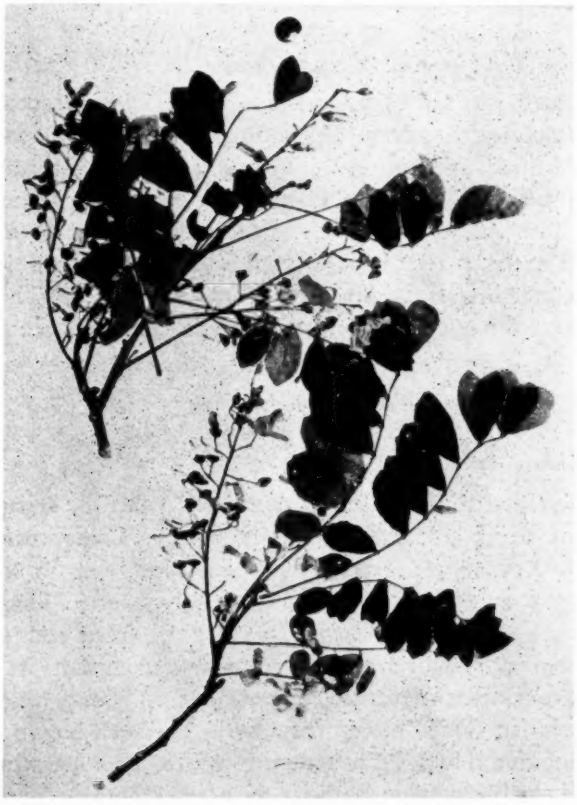

Fig. 1—Derris elliptica (Roxb.) Benth. Leaf and flowering branches, x 1/5.

ing an orbicular standard which is silky externally (most diagnostic feature) and shows two appendicular callosities at its base, 10 monadelphous stamens, a monocarpellary pistil with a simple style and villose ovary. The fruit is a flattened, elliptical legume, narrowly winged along the sutures, from 1 to 3.5 inches in length and containing one to four seeds.

This species was first described by Roxburg [1] in Hortus Bengalensis under the name of *Galedupa elliptica*. He gave its habitat as the Indian Archipelago, Amboyna and the Malay Islands. Later Bentham [2] placed it in the genus *Derris* and listed it under the Section *Paraderris* of the *Leguminosæ*. It has been reported by other writers as occurring in Borneo (Miquel), Java (Zollinger), Siam (Schamburg), Attran and Moolmyne (Wallich), Sumatra (King), and the Philippines (Merrill).

Commercial

The chief commercial sources for this drug are reported to be Malay, Borneo and Sumatra. According to the U. S. Department of Commerce [3] about 2000 acres of Derris are under cultivation in the State of Johore, 1000 in the Federated Malay States and 2000 in Sarawak, Borneo. Great Britain is the largest importer at present.

Georgi and Curtler [4] have investigated the variations in amount of ether extract of *Derris elliptica* root of varying age. Their results show the optimum age for harvesting is when the plants are 25 months old.

Description of Crude Drug

Physical Characteristics

Rhizome and roots of *Derris elliptica* attached or separate or in segments of varying length. Rhizome oblique, sometimes tortuous and branched, usually in segments 2 cm. to 15 cm. in length and 8 mm. to 25 mm. in thickness; externally brown, longitudinally wrinkled and showing numerous circular lenticels and transverse fissures, frequently with a number of roots attached to its posterior and under surfaces; fracture unbreakable in short, thick pieces, tough-fibrous in long pieces; internally reddish-brown to light brown, exhibiting a bark up to 2 mm. in width, a comparatively broad wood and a small central pith, the latter often hollow in longitudinally cut segments. Roots elongated conical and frequently in part adven-

titious from truncated stumps of the rhizomes of cultivated plants, often branched, up to 60 cm. or more in length and 8 mm. in thickness; externally brown, longitudinally wrinkled with scattered warts; internally bark brown, up to about 0.5 mm. in thickness, wood buff; fracture short-fibrous, hazel-switch like, the bark readily separating from the wood and itself separable into layers; odor characteristically aromatic; taste sweet, somewhat licorice like, followed in time by a sensation of numbness.

The rhizome and roots of *D. malaccensis* are purplish-brown to purplish-gray brown externally.

Histology of the Rhizome of Derris Elliptica

Transverse, radial-longitudinal and tangential-longitudinal sections were examined. The cross-section here described was 17 mm.

Fig. 2—Derris elliptica Benth. Leaf and fruiting branch, x 1/5.

in diameter. The rhizome presents for examination, passing from exterior toward the center, the following regions: 1. Cork. 2. Phellogen. 3. Cortex. 4. Pericycle. 5. Phloem. 6. Cambium. 7. Xylem. 8. Pith.

In cross-section, the cork consisted of up to 12 layers of tabular cells with more or less lignified walls. The individual cells were up to 56.02μ in length and 14.18μ in width. Many of them contained a brownish to reddish-brown amorphous content.

The cork cambium (phellogen) consisted of thin-walled meristematic cells. The cortex was extremely narrow, averagely about three layers of cells in breadth, and composed of tangentially-elongated starch parenchyma and scattered resin cells with yellowish-brown content.

Fig. 3—Derris rhizome and root systems, x 2.

The pericycle is composed of a narrow zone of tangentially-elongated starch parenchyma and resin cells through the outermost region of which is an interrupted arc of stone cells of variable shapes and sizes. The stone cells occur isolated and in tangentially-stretched bands. Occasionally a rhombohedral crystal was noticed in the lumen of some of these.

The phloem was very broad and was composed of elongated, conical phloem patches separated by wedge-shaped phloem rays, the latter containing starch grains and resin. Each phloem patch is composed of alternating zones of hard and soft bast, the bast fiber groups being usually more or less surrounded by crystal fibers whose cells contain rhombohedra of calcium oxalate. The individual bast fibers are thick walled, rounded-polygonal to polygonal and vary considerably in degree of lignification, when examined in phloroglucin-HCl.

The cambium is broad and conspicuous for its small, thin-walled cells with protoplasmic contents.

The xylem is about twice the width of the phloem. It is composed of numerous, radially elongated xylem patches separated by starch- and resin-containing medullary rays. Each xylem patch is composed of a matrix of wood parenchyma whose cells are largely filled with starch grains or resin in which matrix are imbedded numer-

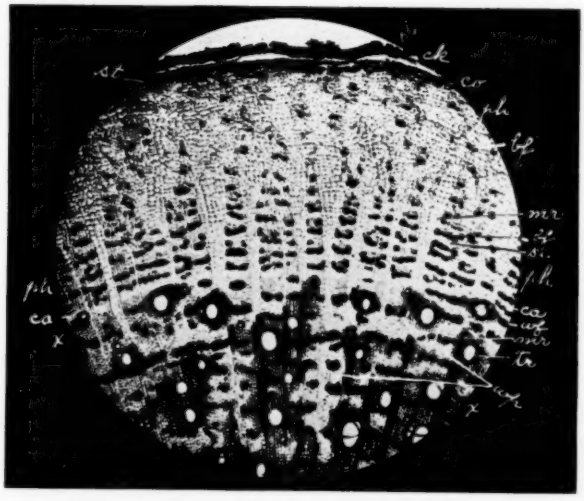

Fig. 4—Photomicrograph of a cross-section of Derris rhizome x 27, showing bark and outer wood regions. ck, cork; st, stone cells; co, cortex; ph, phloem; ca, cambium; x, xylem; bf, bast fibers; mr, medullary rays; sl, sieve tissue; wf, wood fibers; tr, trachea; wp, wood parenchyma.

ous tiers of wood fibers of varying lignification and single, large tracheæ or groups of from two to more rarely five or six of these. The width of these tracheæ is usually up to 129.5μ and serves as a diagnostic factor. The wood fibers vary greatly in extent of lignification and thickness of their walls.

The wood fiber groups are more or less surrounded with crystal fibers containing rhombohedra of calcium oxalate. The xylem rays are composed of radially elongated, parenchymatous cells containing starch and in numerous instances resin. Their walls vary in respect to lignification, some of the cells being non-lignified, others slightly lignified, most lignified. The radial stretches of non-lignified portions of medullary rays in the xylem of Derris, give a broken appearance to the xylem rays in stained sections and, along with the non-lignified character of many areas of xylem cells, provide a striking anomaly.

Radial-longitudinal sections show the crystal fibers to best advantage. These are very numerous in both xylem and phloem, being adherent to bundles of sclerenchyma fibers. The tracheæ are characterized by having simple, slit-like to elliptical pits in their walls. Numerous tracheids with simple pits also occur in the xylem. The bast fibers in this kind of section were thick walled, narrow lumened for the greater part, and possessed pointed ends. Many pursued a

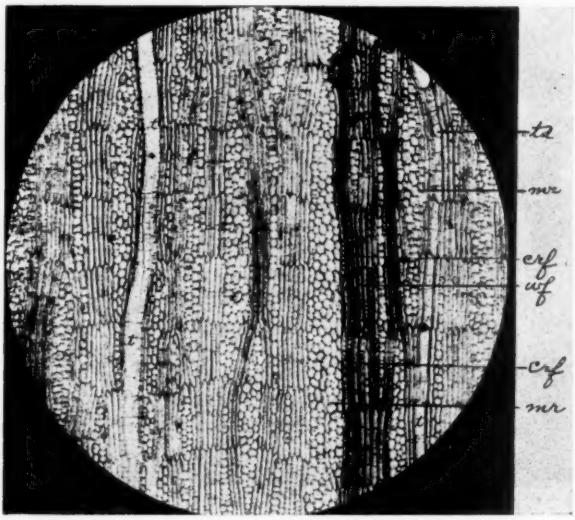

Fig. 5—Photomicrograph of a tangential-longitudinal section through the wood of Derris rhizome, x 53. wf, wood fibers; crf, crystal fibers; mr, medullary rays; tr, tracheae; td, tracheid.

wavy course. The stone cells in the pericycle were rounded, oblong, triangular, ovate, rhomboidal or irregular in shape, and possessed broad lumina and prominent pore canals.

Tangential-longitudinal sections showed the medullary rays to be up to one to seven cells in width. In water mounts the starch cells of the medullary rays appear white in sharp contrast to the yellowish-brown resin cells. The rhombohedral crystals measured up to 21.4μ in diameter or length.

Histology of the Root

The root of Derris presents the following regions for examination, passing from periphery toward the center: 1. Cork. 2. Phellogen. 3. Secondary Cortex. 4. Phloem. 5. Cambium. 6. Xylem.

In general it may be said to bear a somewhat similar appearance to the rhizome when examined in all three types of sections discussed under the histology of that organ, differing mainly from it by its absence of pericycle, primary cortex and pith, the absence of stone cells in the outer region of the bark of *D. elliptica* and its narrower

Fig 6—Transverse section through representative portion of Derris root. ck, cork; co, cortex; ph, phloem; ca, cambium; mr, phloem medullary ray; wf, wood fibers; wp, wood parenchyma; tr, trachea; x, secondary xylem; px, protoxylem. Photomicrograph x 23.

cambium. The root of *Derris malaccensis* possesses groups of stone cells in the secondary cortex.

Powdered Derris

The powder here described was obtained by grinding the roots and rhizome of *D. elliptica.* The powdered drug is reddish-brown It shows, when mounted in appropriate reagents, the following elements: Numerous fragments of bundles of non-lignified and of lignified, thick-walled sclerenchyma fibers with attached portions of crystal fibers containing rhombohedra of calcium oxalate, the rhombohedra being up to 21.24μ in diameter; numerous fragments of reddish-brown cork tissue, the cells of which frequently contain reddish-brown amorphous contents and appear polygonal to rectangular in shape, their walls being more or less lignified; numerous simple, pitted tracheæ and tracheids, the tracheæ having mainly slit-like pores and strongly lignified walls and being up to 148.2μ in diameter; numerous fragments of cortical and of wood parenchyma and medullary rays containing starch and resin; numerous starch grains, the latter being simple, two- to three-compound and occasionally in oval aggre-

Fig. 7—Powdered Derris. a, starch grains; st, stone cells; pt, pitted trachea; td1, pitted tracheids; td2, porous tracheid; f, scelerenchyma fibers; crf, crystal fibers; cr, rhombohedra of calcium oxalate; k1, cork in surface view; k2, cork in transverse view; mr, medullary ray cells; wp, wood parenchyma; cp, cortical parenchyma.

gates, the simple grains varying from spheroidal to spheroidal and beaked at one end, to plano-convex, elliptical and polygonal and measuring up to 17.7μ in diameter or length; stone cells relatively few with moderately thickened, lignified walls, large lumen and usually distinct pore canals and occurring in a wide variety of shapes including elliptic, triangular, rectangular, polygonal, circular and irregular modifications of these. They measured up to 47μ in length, their walls being up to 4μ in thickness.

Further studies are in progress on the rhizome and root of *Derris malaccensis* which will be reported in a subsequent article.

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TINCTURE OF FERRIC CHLORIDE

By Arthur Osol, M. Sc.*

Introduction

Methods of preparation and analysis of tincture of ferric chloride have undergone several important changes in successive revisions of the United States Pharmacopœia, shown in the following brief resumé:

The Pharmacopœia of 1820 directs the preparation to be made from precipitated iron carbonate, muriatic acid and alcohol, no method of assay being given. The first, second and third revision formulas differ only in the quantities of the same components.

The Pharmacopœia of 1860 introduces a new method of preparation, iron in the form of wire being dissolved in muriatic acid, oxidized by nitric acid and mixed with alcohol. For the first time, a method of assay is given, the iron content being determined gravimetrically by precipitation as the hydroxide.

A mixture of solution of ferric chloride and alcohol is given in the formula of the fifth revision (1870).

The 1880 edition uses the same liquids, but also directs that the tincture be stored for three months before use. A test for ferrous iron first appears in this revision.

The seventh revision (1890) directs attention to the reduction of the ferric salt after exposure of the tincture to daylight and includes the precaution of protecting it from light. In this revision, the gravimetric assay is replaced by a volumetric iodide method similar to the present pharmacopœial assay except that no provision is made to include, in the analysis, any iron which may be present in the ferrous condition.

The eighth, ninth and tenth revisions retain the formula using solution of ferric chloride and alcohol, but introduce changes in the directions for assaying and storing. In order to include ferrous, as well as ferric iron, the eighth revision assay method provides for the oxidation of ferrous iron by first evaporating the tincture to dryness and subsequently treating the residue with hydrogen peroxide and hydrochloric acid before carrying out the assay proper. This assay has been retained in the ninth and tenth revisions. The U. S.

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P. IX also introduces the precaution of preserving the tincture in amber-colored bottles. In the U. S. P. X we find that the three months' storage requirement is discontinued.

Finally, J. C. Krantz, Jr., proposes for the eleventh revision a simplified assay in which the preliminary peroxide treatment is omitted. As chairman of Sub-Committee No. 7 of the Pharmacopœial Revision Committee, he reports the following: (1) "The work in this laboratory indicates that this method is far more accurate than the method as recognized by the present revision of the Pharmacopœia. For a series of fifteen assays on a standard sample of Tincture of Ferric Chloride, carried out by auxiliary member Margarethe Oakley and the chairman, the probable error of an individual determination by the Pharmacopœia method was plus or minus fifty-four thousandths per cent. By the modified method the probable error was plus or minus nineteen thousandths of one per cent. We, therefore, recommend this simpler and more accurate method of assay for Tincture of Ferric Chloride."

It is well known that iron in tincture of ferric chloride is reduced on exposure to sunlight. In cognizance of this fact, it would be of interest to determine the extent of reduction under varying conditions of exposure, both normal and abnormal. Accordingly, portions of a tincture were exposed to sunlight and to ultra-violet radiation; and to determine the effect of alcohol on this reduction an aqueous solution of ferric chloride was also exposed.

With few exceptions the following experiments were performed on portions of one sample of tincture of ferric chloride, made by the U. S. P. X procedure, and preserved in an amber-colored, glass-stoppered bottle kept in a cool, dark place. This tincture will be designated as sample "A." Two other tinctures, designated "B" and "C" were assayed. Sample "B" had been prepared for over twelve months, sample "C" approximately six months; both were preserved in amber-colored, glass-stoppered bottles.

Experimental

All samples were found to contain some ferrous iron when tested with potassium ferricyanide. In order to determine such small amounts quantitatively the following procedure was used. To each of several 5 cc. portions of tincture were added about 10 cc. of water and two or three drops of concentrated hydrochloric acid followed

by varying quantities of tenth-normal potassium dichromate solution starting with 0.05 cc. and increasing by 0.05 cc. Upon addition of potassium ferricyanide T. S. to each portion the minimum quantity of potassium dichromate necessary to oxidize the ferrous iron may be determined by observing which portion first shows neither a blue nor green color. The determination may be made upon smaller samples of tincture if desired, however, the quantity of ferrous iron in properly stored tinctures is so small that it is advisable to use either 5 cc. portions of tincture or to use a more dilute solution of potassium dichromate. In this manner it was found that sample "A," for instance, required but 0.1 cc. of tenth-normal dichromate to oxidize the ferrous iron, a quantity equivalent to 0.011 per cent. Fe.

The three samples were next assayed by the U. S. P. X method and also by Krantz's proposed modification. The latter method is as follows: "Transfer 5 cc. of tincture of ferric chloride accurately measured to a flask of suitable capacity. Add about 20 cc. of distilled water, 3 gm. of potassium iodide and 3 cc. of hydrochloric acid. Titrate the solution with tenth-normal sodium thiosulphate, using starch T. S. as an indicator. Each cc. of tenth-normal sodium thiosulphate corresponds to 0.005584 gm. of Fe."

The accompanying table contains the results of these assays. It is to be noted that although the results of Krantz's method are expressed in grams of iron per 100 cc. they are nevertheless directly comparable to the results obtained by the U. S. P. method, the specific gravity of each tincture having been found to be approximately one.

TABLE I

Sample.	*U. S. P. X Method* *Per Cent. Fe.*	*Krantz's Method* *Gm. Fe per 100 cc.*	*Ferrous Iron* *Per Cent. Fe.*
"A"	(1) 5.17	(1) 5.22	0.011
	(2) 5.21	(2) 5.18	
		(3) 5.21	
"B"	(1) 4.34	(1) 4.38	0.017
		(2) 4.37	
"C"	(1) 4.81	(1) 4.79	0.023
		(2) 4.81	

It is evident from the above that the results obtained by both methods are identical.** This was to be expected as the tinctures

**In a subsequent paper the author will present the results of similar experiments on the methods of analysis and decomposition of Tincture of Ferric Citrochloride, N. F. V.

contain negligible quantities of ferrous iron. However, tinctures containing appreciable quantities of ferrous iron could not be expected to yield identical results as the iodide reacts only with ferric iron. The problem resolves itself therefore in determining the quantity of ferrous iron which may be formed under varying conditions of preservation of the tincture.

In order to determine the extent of reduction of iron upon exposure of a tincture to sunlight, one portion of sample "A" was exposed in a clear-glass bottle and another in an amber-colored bottle for a period of one week. The exposed tinctures were then assayed by the two methods mentioned above and the ferrous iron content directly determined by the dichromate method. The results of the analyses are tabulated in Table II.

TABLE II

	U. S. P. X Method	*Krantz's Method*	*Ferrous Iron*
Container	*Per Cent. Fe.*	*Gm. Fe per 100 cc.*	*Per Cent. Fe.*
Clear-glass	5.21*	4.05*	1.20
Amber-colored	5.23	5.20	0.057

*Strong acetaldehyde odor noticeable on removing stopper.

Several conclusions may be drawn based upon the results of Table II. First, appreciable quantities of ferrous iron are formed upon exposing tincture of ferric chloride to sunlight, in clear-glass bottles. Second, the use of amber-colored bottles prevents such reduction almost entirely, and third, tinctures exposed to sunlight can be assayed for total iron only by the U. S. P. X method, the results by Krantz's method of analysis reporting only the ferric iron content.

The intensity of sunlight being a variable quantity, the use of ultra-violet radiation to study the rate of reduction was suggested. After some experimentation, in which portions of sample "A" contained in stoppered quartz test tubes were rayed using a Hanovia quartz mercury vapor lamp, it was found that the rate of reduction of iron was only roughly proportional to the time of raying, and that the results could not be duplicated within the experimental error. In all samples of tincture which had been exposed to ultra-violet radiation a distinct odor of acetaldehyde was noticeable, as well as some gas evolution. It has been pointed out in the literature that both alcohol and acetaldehyde are decomposed by ultra-violet light with the formation of carbon monoxide, hydrogen and hydrocarbons.

(2) It is therefore probable that the introduction of side reactions explains the lack of better agreement in the results.

In order to determine the effect of alcohol on the reduction of tincture of ferric chloride, an aqueous solution was prepared containing the same percentage of ferric chloride as sample "A." Portions of this aqueous solution and of the tincture "A," placed in quartz test tubes, were exposed to ultra-violet, the results being given in Table III.

TABLE III

Preparation.	*Per Cent. Iron Reduced After Two Hours.*	*Per Cent. Iron Reduced After Four Hours.*
Aqueous solution of ferric chloride (5.2 per cent.)	0.017	0.029
Tincture of ferric chloride "A" (5.2 per cent.)	1.25	2.23

Acknowledgment

The author is indebted to Professor Frank X. Moerk for many valuable suggestions in connection with this work.

Summary

(1) Several samples of tincture of ferric chloride have been analyzed by the U. S. P. X method of assay and by the method proposed by J. C. Krantz, Jr. The latter method has been found to give results identical with those obtained by the U. S. P. method when the tincture contains negligible quantities of ferrous iron; a condition which is attained in properly stored samples of tincture of ferric chloride.

(2) It has however been shown that, in samples of tincture of ferric chloride, which contain appreciable quantities of ferrous salt, the determination of total iron by the iodide method must be preceded by oxidation of the reduced iron.

(3) The analysis of portions of tincture exposed sunlight in clear and amber-colored bottles has shown that appreciable reduction of iron is observed in the sample exposed in a clear-glass bottle, while almost no reduction is observed in the sample exposed in an amber-colored bottle.

(4) Portions of tincture exposed to ultra-violet radiation develop considerable quantities of ferrous iron, a rough proportionality existing between time of raying and amount of ferrous iron formed.

(5) Aqueous solutions of ferric chloride show very little reduction of iron after exposure to ultra-violet light.

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A NOTE ON THE COMPARISON OF THE PHYSIOLOGICAL ACTIVITY OF FLUID EXTRACTS OF ERGOT AS DETERMINED BY THE COCK'S COMB AND COLORIMETRIC METHODS*

By Tillman D. Gerlough

IT SEEMS unnecessary to state that there is an urgent need for a simple and rapid chemical method which will yield a reliable measure of the physiologically active alkaloid or alkaloids of fluid extract of ergot. Only recently has a method been developed by Smith,[1] which appears to fulfill these requirements. The method is a colorimetric one based upon the reaction between p-dimethyl amino benzaldehyde and the ergot alkaloids. Under the influence of sunlight a relatively stable blue color forms, the depth of which is practically proportional to the concentration of the alkaloid.

The major criticism of the method is a common one, viz., lack of definite information as to whether or not the reaction is specific for the physiologically active substances. In the report submitted by Smith, 5 samples of fluid extract of ergot were assayed by the physiological method of Broom and Clark,[2] and compared against the results obtained by the colorimetric method. The agreement between the results of both methods was indeed gratifying. The colorimetric values were 5 to 10 per cent. higher than those obtained by the Broom and Clark method. However, it was clearly recognized by Smith that the colorimetric method may not in all instances give a true measure of the physiological activity. In fact, he demonstrated that while crystalline ergotinine and ergotaminine give practically the same amount of color as ergotamine tartrate, yet physiologically, these compounds were only one-tenth as active.

Although the latter experiment casts some doubt on the specificity and, therefore, the value of the colorimetric method, at the same time the question naturally arises as to what extent physiologically inactive isomers in fluid ergot preparations actually alter the colorimetric values. In this connection the remarks of Smith are pertinent,—"Since it is not known to what extent, if any, the latter (ergotaminine and ergotinine) occur in ergot preformed, or in the official extract, the value of the present chemical method can be deter-

*Contribution from the Biological Laboratories of E. R. Squibb & Sons, New Brunswick, N. J.

mined only by an exhaustive comparative study of the two methods as applied to a large series of fluid extracts . . . ."

From the actual results obtained by Smith on 5 fluid extracts, it appears that the presence of the supposed inactive isomers is of little consequence. That a good evaluation of potency may be obtained by the colorimetric method is further substantiated by a later and more extensive comparative examination conducted by Smith and Stohlman [3] on 38 samples of fluid extracts of widely different strengths. The average percentage deviation of the colorimetric values from those obtained by the Broom and Clark method was 14.8 per cent. The agreement was considered very satisfactory in most cases.

It is extremely desirable to know to what extent results obtained by the colorimetric method compare with those of the U. S. P. Method (cock's comb). Although Smith and Stohlman have made such an examination on 14 samples their results however do not permit strict comparison because the colorimetric values were determined 6 to 7 months after the U. S. P. assay. There is reason to believe, as some of their other results show, that loss in potency may occur during that period.

Pursuing the investigation along the general line suggested by Dr. Smith, a comparative examination by his chemical method and the cock's comb method, was made in this laboratory on 24 samples of fluid ergot. The material represented not only extracts made by standard procedures, but also experimental samples in which the conditions of extraction and purification were altered.

The results are tabulated in Table I. It should be mentioned that both sets of results were obtained in an entirely independent manner by different individuals. The standard employed for both was the U. S. P. X Standard Fluid Extract of Ergot, No. 2160, supplied by the Food and Drug Administration of the Department of Agriculture. Each physiological value, column 3, is an average obtained from the injection of a given sample in 20 to 40 birds. In making the test a like number of birds were injected simultaneously with standard sample No. 2160. Without going into details, the basic steps of Smith's colorimetric method are briefly this: (1) extraction of alkaloids from alkaline ergot solution with ether; (2) removal of yellow pigments from the ethereal extract by washing with very dilute ammonia water; (3) subsequent extraction of alkaloids from the washed ether solution by one per cent. tartaric acid; (4) colorimetric determination of alkaloid in the tartaric acid solution after reaction

with p-dimethyl amino benzaldehyde. The color thus produced was compared in our determination with that of the standard ergot extract referred to above treated in identical manner throughout rather than by direct comparison with pure ergotamine tartrate.

The percentage deviation of the values obtained by the chemical method from those of the cock's comb are given in column 4. It can be seen that the deviation in one instance was as high as 39 per cent. The average, however, is 16.2. It is possible that the discrepancies are to be attributed in some cases to the physiological results obtained rather than to any preponderance of an inactive color producing isomer of active ergot alkaloid. On the whole, there is reasonable agreement between both methods.

At present, the chief value * of the colorimetric method lies in the fact that it furnishes a good estimate of potency, which, if used in conjunction with the physiological assay will eliminate considerable preliminary testing. Its general acceptance, however, will rest, to major extent, upon the agreement of comparative observations obtained in the hands of other investigators. We feel justified, therefore, in presenting our results as a step in this direction.

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*The method may find useful application in an extensive investigation dealing with the factors which regulate the stability of the active material. For example, many determinations could be conducted rapidly after the ergot solutions had been subjected to a wide range of conditions such as the effect of temperature, light, pH, purity, presence of gases, alcohol, etc. After the general trend of change had been established colorimetrically, then a few of the most important solutions would be selected for verification by physiological assay.

TABLE I

Comparison of Activity of Fluid Ergots Determined by Colorimetric and Cock's Comb Methods

Sample No.	Per cent. U. S. P. X Colorimetric	Per cent. U. S. P. X Cock's Comb	Per cent. Deviation from Cock's Comb Method
1.	96	108	11.1
2.	75	61	22.9
3.	92.5	114	18.8
4.	117	145	19.3
5.	122	153	20.2
6.	113	113	0.0
7.	101	89	13.5
8.	23.1	23	0.4
9.	134	116	15.5
10.	83	70	18.6
11.	58	52	11.5
12.	77	83	7.2
13.	46.5	73	34.7
14.	54	58	6.9
15.	58	95	39.0
16.	75	91	17.6
17.	38	31	22.2
18.	145	200	27.5
19.	34	36	5.5
20.	171	142	20.5
21.	156	201	23.3
22.	160	196	18.4
23.	15	13	15.4
24.	125	124	0.8
		Av.	16.2

THE STORY OF ALCOHOL *

By C. Clifton Pines

THE word "alcohol" has a curious history. It belongs to a class of words, among which are "alkali" and "alchemy," that have come to us from the ancient Arabic philosophers. The original application of the word was far different from the present meaning. The Arabic form, which may be transliterated as "al kohl," designated a finely-powdered black substance, possibly stibnite (native antimony sulphide), or galena (native lead sulphide), used for staining the eyebrows and eyelashes.

ALCOHOL A COSMETIC

The humorist might say that alcohol still has cosmetic uses as it sometimes aids in painting the town red, but this need not be considered here. From the original meaning, the term was extended to any finely-divided material and for many centuries it was essentially indicative of minute division. Even as late as the early part of the nineteenth century, Sir Humphrey Davy, an English scientist (1778-1829), spoke of the "alcohol of sulphur," meaning the finely-divided form, "precipitated sulphur." The old term in pharmacy, "alcoholized iron," is still used to signify a finely-divided iron. From signifying fine division it came by a not unnatural transfer to mean a vapor or spirit.

Today the word has been extended by chemists in another way, being used to designate atomic arrangement, and many "alcohols" are known, some agreeing closely with ordinary alcohol, as to properties, others being different. The so-called wood alcohol is of the first type, glycol and glycerin of the second.

AQUA ARDENS

Ethyl alcohol, scientifically named ethyl hydroxide or ethanol and commonly called grain or molasses alcohol, is our most important alcohol. Other names referring to ethyl alcohol are Aqua Vitæ, Aqua Ardens, Aqua Vini, Spirits of Wine, and Cologne Spirits. It is occasionally found in nature but it is easily formed by the alteration of various vegetable substances. It has been known from the most remote times. The first recorded scientific discovery of isolated alcohol was that of an Arabian chemist, Albucasis, who practiced distillation in the twelfth century, although distillation was first practiced shortly after the beginning of the Chris-

*One of a Series of Popular Science Talks given at the Philadelphia College of Pharmacy and Science, 1931 Season.

tian Era in Alexandria, but no definite record occurs, telling of the isolation of alcohol itself, at that time. Albertus Magnus (1193-1280), about 1250 A. D., was one of the first authors to intelligently describe the concentration of alcohol by distillation.

THE FIRST STILL

About the time of Albertus Magnus, a book called the "Book of Fires" tells how to make Aqua Ardens as follows: Take best old wine of any color whatsoever in a cucurbita and alembic with joints well luted and distil with gentle fire. That which distils is aqua ardens. The term "alcohol" was applied to the "spirits of wine" in the sixteenth century. Lavoisier (1743-1794), a French chemist of note, arrived at the qualitative, and deSaussure in 1808 at the quantitative composition of alcohol. Curiously enough ethyl alcohol is said to have been synthesised by an English apothecary named Henry Hennel in 1826, two years before the epoch-making synthesis of urea from ammonium cyanate by Wöhler.

NOAH KNEW IT

Alcohol was unknowingly prepared centuries ago as one of the products of fermentation of the sugars in the grape. According to the Bible, Noah knew it. Grapes were crushed, often being trodden under foot, and the juice which resulted was collected in vessels and allowed to ferment. The plants which ferment the acid juice are the yeasts, several varieties of the Saccharomyces ellipsoideus, a wild species occurring naturally on the skin of the grape. Before the time of Pasteur (1822-1895), fermentation was believed to be spontaneous, but he showed that it was brought about by the naturally occurring yeast plants. When grape sugar ferments alcohol, carbon dioxide, glycerin, succinic acid and some "fusel oil" are formed. Wine, the product of the yeast plant can never contain more than 14 per cent. of alcohol because a higher amount kills the yeast. Although grapes were fermented in prehistoric times to make wines, mead, one of the earliest fermented beverages known to tradition was also prepared. Mead was made from the honey water, the washings of the honey comb. Honey contains the fermentable sugar levulose or fruit sugar.

CEREAL BEVERAGES

Cereals such as barley were likewise fermented to make beverages containing alcohol as one of the products of fermentation. Barley is used in making malt, the first step in preparing the grain for fermentation. In barley

and in other grains as well, starch is found in considerable quantity and during malting which consists in steeping the barley in water and then drying, when under the proper temperature conditions, germination (sprouting) takes place and an enzyme diastase is formed which acts on the starch changing it to maltose, a sugar, and dextrin. The malt (sprouted barley) is next fermented by yeasts which change the maltose into alcohol, carbon dioxide and a few other substances.

To obtain alcohol proper from wine distillation must be resorted to and in the past alcohol has been obtained by distilling the fermented fruit juices, not only of the different varieties of grapes, but of the prune, peach, apricot, cherry, and other fruits. Likewise in the case of the fermentations of grains, besides barley, rye, wheat, corn, and rice have furnished the starches to be turned into sugars which the yeasts subsequently change into alcohol and carbon dioxide in the main. For many years alcohol was obtained from grain, hence the name "grain" alcohol.

INDUSTRIAL ALCOHOL

At the present time alcohol, now called "industrial" alcohol because of its wide use in the industries, is obtained from the cheapest raw material at hand. About 90 per cent. of the alcohol used in the industries is manufactured from molasses, a by-product of the sugar refinery. A great deal of the molasses comes from Cuba to the United States on large tankers. These tankers are used to transport nothing but molasses, by the big alcohol manufacturers, so as to guard against the possibility of contaminating this raw material with any other substances. The tankers have a capacity of about 2,000,000 gallons. A ship is unloaded by means of powerful pumps which pump the molasses into large storage tanks through pipe lines. About thirty-three hours is required to empty a tank ship.

The production of alcohol, in general, by fermentation involves three steps: (1) changing the raw material to fermentable sugars; (2) fermentation, and (3) distillation. The first step is required when starch or starch containing materials are used, but when blackstrap molasses is the raw material to be used, sugar is the main constituent so that the first step is unnecessary, thus simplifying the operation.

The propagation and culture of yeast is the most important phase of the fermentation step because maximum yield in the conversion of sugar to alcohol requires a strain of yeast best adapted to the raw

material to be fermented. An outstanding characteristic of the action of yeast is that this organism tends to overgrow all other organisms so long as sugar is present. Yeast also grows as was mentioned under the fermentation of grape juice, in an acid medium while most other organisms are inhibited in their growth by acid. In using cane sugar molasses sulphuric acid is added to bring the pH to approximately 5.0. This pH (hydrogen ion concentration) inhibits the growth of objectionable organisms and fortunately, it is favorable for the activity of the yeast.

Distillation, the final step in the production of alcohol, will be considered later.

Some alcohol is today manufactured from grain. Indian corn in admixture with about 10 per cent. malt is fermented and on distillation true grain alcohol is obtained. In order to produce alcohol for the industries as cheaply as possible, other raw materials have been tried, many on a practical scale. Among the materials tried were cull potatoes, cull fruits, cull sweet potatoes, cannery wastes, cassava roots, and even garbage. Because of economical problems, none of the materials mentioned are used commercially, but other waste materials, such as saw-dust and wood refuse from different sources are used, and alcohol (ethyl alcohol) from wood is now being made in plants which distill about 3000 gallons daily. Soft woods yield the most alcohol and coniferous woods are generally used. In a well-designed plant about twenty gallons of 190 proof (95 per cent. by volume) is obtained from a ton (about one cord) of the dry wood.

SYNTHETIC ETHANOL

During the year 1930 ethyl alcohol was produced synthetically from ethylene on a commercial scale. Ethylene can be obtained from many substances rich in carbon as coal and petroleum oils. In this process, the ethylene is mixed with concentrated sulphuric acid and at a temperature of 160° C. ethyl sulphuric acid is formed; this when boiled with water yields ethyl alcohol. This method was discovered by Faraday (1791-1867), an English scientist and corroborated in 1855 by Berthelot (1827-1907), a French chemist.

Acetylene, the gas formed when water is added to calcium carbide, may be used also in the synthetic production of alcohol. Calcium carbide is made by heating a mixture of coke and lime in the electric furnace. In this process, the acetylene is led into a hot concen-

trated solution of sulphuric or phosphoric acid (the catalyst), containing a dissolved mercury salt which functions as a promoter. (A promoter is a substance which acts by catalyzing a catalyst.) Acetaldehyde is the product of the foregoing reaction and by hydrogenation of the aldehyde, ethyl alcohol is produced. The hydrogenation is effected by leading a mixture of hydrogen and the aldehyde over a suitable catalyst, such as finely divided nickel. Methyl alcohol (wood alcohol or methanol) usually obtained by destructive distillation of wood, has been, within the last few years, produced synthetically, by a method similar to the above process. The procedure in making methyl alcohol consists in passing a mixture of hydrogen and carbon monoxide over a catalyst, composed chiefly of zinc oxide, with other oxides present as promoters. Methanol forms by direct union.

The amount of alcohol produced during 1930 from ethylene was 50,000 proof gallons. Production of pure alcohol (ethyl) is given in proof gallons or tax gallons. When alcohol is denatured, and by denaturing is meant, the addition of a substance or substances to the pure ethyl alcohol making it unfit for beverage purposes, it is then measured by the wine gallon. A wine gallon is a measure of quantity (231 cubic inches) of any proof. In the United States the wine gallon consists of eight pints of sixteen fluid ounces each or a total of 128 fluid ounces. United States "proof spirit" refers to a diluted alcohol containing 50 per cent. by volume of absolute (100 per cent.) alcohol at 15.56° C. A proof gallon is a wine gallon of 100 proof spirits, one, containing 50 per cent. of alcohol by volume. Alcohol as generally produced for commercial purposes ranges from 188 to 192 proof or percentage by volume between 94 and 96. Records of production and disposition in statistical tables show the proof content for taxing purposes, while denatured alcohol, which is sold without government tax, is shown by the wine gallon. The reader, therefore, should keep in mind that a wine gallon of absolute alcohol is practically 100 per cent. alcohol by volume and is equal to two proof or tax gallons because each proof gallon contains 50 per cent. alcohol by volume. A wine gallon of 190 proof (95 per cent.) spirits is equal to 1.9 proof or tax gallons.

The third and final step in the manufacture of commercial or industrial alcohol is distillation. The product of the fermentation of the sugar containing materials, which is called by distillers, the mash or wort, contains alcohol in strength from 5 per cent. to 10 per cent., usually from about 5 per cent. to 7 per cent. To obtain

the alcohol, distillation is resorted to. The fermented mash or liquid filtered from the mash is heated in a still and a crude alcohol 50 per cent. to 75 per cent. in strength is obtained. The crude alcohol is then distilled from a refining still and by this second step, one of rectiffcation, an alcohol of about 95 per cent. by volume is obtained. In modern practice the two stages are sometimes combined and carried out in one continuous distilling unit consisting of several columns.

THE STRONGEST ALCOHOL

During the last few years anhydrous ethyl alcohol, the so-called absolute alcohol, has been placed on the market in commercial quantities. This alcohol is about 100 per cent. in strength by volume (99 per cent. by weight). Absolute alcohol had been used in small quantities for quite a number of years, especially in the manufacture of organic chemicals, but it was then somewhat of a chemical curiosity—now present-day methods of manufacturing have made it available in tank car quantities. Then it sold for from $10 to $20 a gallon. It now sells for less than one dollar a gallon. Formerly, it was made from 95 per cent. alcohol by removing the 5 per cent. of water with quicklime, but today it is manufactured by a physical-chemical method which is an exclusive and patented distillation process. One method used for making absolute alcohol is the distillation of a mixture of benzene, alcohol and water. This system has a constant boiling mixture, boiling at a temperature below any of the pure components and containing more water than the constant boiling mixture of alcohol and water. The process has been so perfected that absolute alcohol can be distilled continuously from the mixture of benzene, alcohol and water.

At the present time alcohol for use in the arts and industries may be obtained as pure ethyl hydroxide known as absolute or dehydrated alcohol (100 per cent. by volume) and pure alcohol (95 per cent. by volume). Denatured alcohol is made from either or both of the strengths just enumerated by the addition of suitable denaturing agents.

ONE OF THE FOUR HORSEMEN

Alcohol, either pure or denatured, is the most useful solvent next to that of water which is used today. It mixes with water in all proportions, sometimes with a fair shrinkage in volume. For example, when making official diluted alcohol which is used pharmaceutically, 95 per cent. alcohol is mixed with an equal volume of distilled water and a

shrinkage in volume of the finished dilution is noted. Thus, 50 ounces of alcohol added to 50 ounces of water would be expected to yield 100 ounces of diluted alcohol, but only 96¼ ounces are obtained which shows a shrinkage of 3¾ ounces—not much loss in volume when diluting small quantities of alcohol, but when gallons are diluted the shrinkage is considerable and must be taken into account. Besides acting as a solvent, it unites chemically with many substances, forming hundreds of new compounds. Of interest in this connection is the so-called alcohol of crystallization in which the alcohol acts similarly to water and combines with salts, forming crystalline compounds. Alcohol as a chemical reactant is second only to sulphuric acid and as one of the "Four Horsemen" of the arts and industries, is a "key" chemical of our present civilization along with sulphuric acid, caustic soda and water.

The most outstanding use of alcohol from the humanitarian standpoint is in the manufacture of ether. Ether was known since the thirteenth century, being made by the action of sulphuric acid on alcohol; however, it was not used for the elimination of pain during operations until 1842. Strangely enough, a number of other anæsthetics are derivatives of ethanol-chloroform first prepared in 1831, ethyl chloride, ethylene, and tribrom ethyl alcohol, the last named is a recent addition to the list, although ethylene has been used as an anæsthetic only the last seven years. Ethyl alcohol is used in making antiseptics such as iodoform, tincture of iodine and mercurochrome, and in the making of thousands of medicinal preparations, some of the best known being sweet spirits of nitre, aspirin, paregoric, camphor, acetanilide, insulin and salvarsan.

Around, in and over the automobile, alcohol has many important uses. It is put into the radiator and mixed with water forms the common anti-freeze solution. In Brazil, alcohol blended with ether is used as a fuel, and in other countries absolute alcohol blended with gasoline is used in the gas tank. It is claimed to be a much cheaper motor fuel than gasoline, for it burns more efficiently than the latter and thus may actually furnish more miles to the gallon, and because of its efficient burning no troublesome deposits of carbon are formed. Tetraethyl lead, the compound present in the "ethyl" gas, requires alcohol in its manufacture. In the refining of rubber for making automobile tires, in the making of non-scatterable glass and in the production of the imitation leather for the interior and the top as

well as for the lacquer used in finishing the metal parts of the automobile, alcohol is required in large quantities.

Alcohol in and about the home has a great number of uses. As solidified or solid alcohol, it is used in small stoves for cooking purposes. It enters into the manufacture of gas mantles, varnishes, lacquers, shellacs and enamels. In other countries than ours, it is used for lighting the home and even for street lighting. Employing the ordinary gas mantle, it has been found that alcohol will give three and one-half times as much light measured in candlepower-hours as an equal quantity of kerosene burned in a good kerosene lamp. Celluloid, pyralin, and commercial articles of like nature, require alcohol in their manufacturing process. Alcohol is used as a solvent for dyes, confectioner's colors and gelatin food products. It is used in making some kinds of inks.

In times of war alcohol is a necessity and an alcohol plant is really a potential munitions plant, for in the construction of a twelve-inch shell nearly a barrel of it is used. TNT, smokeless powder, and cordite (a kind of smokeless powder), all require alcohol in their manufacture. Acetone used in large quantities in war times can be made in large quantities by changing alcohol to acetic acid, acetic acid to calcium acetate and calcium acetate to acetone. This process, although costly, was actually operated during the World War because the acetone was an absolute necessity in the production of cordite, the explosive used by the British in their artillery and rifles. Of interest during the late war was the order by General Pershing in 1918, demanding 1000 tons of mustard gas a day, to be delivered immediately. To produce a ton of mustard gas a day requires a ton of alcohol; hence at that time to arrange for filling this enormous order, the entire distilling industry of the United States was mobilized for the production of nothing but alcohol.

The quantity of alcohol used by the industries in the United States has steadily and markedly increased, from year to year. In 1906, Congress passed the first denatured alcohol act, or as it is known, the tax-free industrial alcohol act, United States being the last large country to recognize and foster the industrial use of alcohol by relieving it from burdensome taxation. England as far back as 1855, denatured alcohol for industrial use, while France and Germany had also extensive chemical industry development due to the use of industrial alcohol prior to 1906.

TAX-FREE ALCOHOL

In 1907, the year after the government tax was removed, about a million and a half gallons of industrial alcohol were used. At the present time about one hundred million gallons is used yearly. The World War caused increased consumption over the ten preceding years and in 1917 about fifty-six million gallons were used. Of the alcohol consumed during the past year, motorists poured more than 35,000,000 gallons into their automobile radiators in making anti-freeze solution. Nearly 9,000,000 gallons were used in the manufacture of lacquers. More than 1,000,000 gallons were required in the production of imitation leathers. More than 1,000,000 gallons were bottled as bathing alcohol. The makers of shellacs, varnishes and paints required 5,000,000 gallons more. In the making of vinegar more than 9,000,000 gallons were used last year. Toilet water preparations, perfumes and cosmetics required about 2,000,000 gallons during the year 1930.

Many of us think of alcohol only in connection with the Eighteenth Amendment and learn only about the illegitimate uses of it from the daily press, whereas alcohol has thousands of legitimate and worthwhile uses, being the basic chemical for more than 25,000 manufacturers who make the aspirin or the imitation silk, the chloroform or the vinegar, the ether or the insulin, the photographic films or the metal polishes, the vacuum tubes or the non-scatterable glass and the myriad articles which are today a necessary part of our daily lives.

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ABSTRACTED AND REPRINTED ARTICLE

THE MEDICAL ASPECTS OF PROTEIN DISTURBANCES*

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Claude Bernard claimed, about sixty years ago, that anesthesia was due to the reversible coagulation of some of the proteins of the brain and of the sensory nerves. It is now recognized that he was right and that his conception of the medical aspect of protein disturbances is of immense importance. Claude Bernard's point of view enables us to account for the action of anesthetics, narcotics, hypnotics, caffeine, histamine, strychnine, curare, and potassium salts. It has already given us a working theory of insanity and will undoubtedly increase our understanding of immunity reactions and anaphylaxis. It is throwing an entirely new light on medicine, physiology, psychology, and pharmacology.

. . . . . .

The predominant theory of anesthesia has been the Overton-Meyer theory, which postulated that an anesthetic is lipoid-soluble and that its anesthetizing power is connected with the distribution ratio between the lipoids and the blood. Since it is not true that everything that goes into the brain cells through the lipoid membranes is an anesthetic, and since the theory in thirty years never got beyond the problem of anesthesia, people began to wonder whether the Overton-Meyer theory were anything more than a theory of transport, which accounted for certain substances getting into certain cells. Clowes believes that solubility in lipoids is the important thing because it disturbs a complex equilibrium. That is so vague as not to be helpful and gets us into trouble if we try to account for the action of anesthetics, narcotics, hypnotics, caffeine, histamine, strychnine, curare, potassium salts, and anaphylactic shock. So far as we now

*Dohme lecture delivered at The Johns Hopkins University, May 15, 1931. Reprinted from *Jour. Chem. Education*, December, 1931.

know there are not enough lipoids or combinations of lipoids to make it possible to account for these varied actions on the basis of selective solubility in different lipoids in different parts of the body. In addition, anaphylactic shock is almost certainly primarily a protein problem.

About sixty years ago the distinguished French physiologist, Claude Bernard, advanced the view that anesthesia was due to the reversible coagulation of the colloids of the brain and the sensory nerves. By that he really meant the proteins of the brain and the sensory nerves, because the anesthetics do not coagulate the lipoids. This theory was rejected for two reasons: that the concentrations necessary to coagulate the nerve proteins were much higher than those occurring in anesthesia; and that the coagulation by anesthetics was irreversible. The articles on the theory of anesthesia refer to this hypothesis by Claude Bernard as an utterly worthless one. As a matter of fact, Claude Bernard was right and the other people were wrong. Neither Claude Bernard nor anybody else knew enough colloid chemistry to see the flaw in the argument; but the flaw was there. It is true that relatively high concentrations of alcohol, for instance, are necessary to coagulate a moderately pure, negatively charged sol—40 per cent. by volume in the case of copper ferrocyanide. If we add nearly enough electrolyte to precipitate the copper ferrocyanide sol, we can make the amount of alcohol necessary to precipitate as small as we please. If calcium chloride is added to a negatively charged albumin sol, one drop of the common alcohols or a small crystal of chloral hydrate is sufficient to coagulate the albumin. Under these conditions, the coagulation is reversible. The two apparently serious objections to Claude Bernard's theory are thereby eliminated, because there are always electrolytes in contact with the tissues.

For the time being Claude Bernard's theory is that reversible coagulation of the sensory nerves gives rise to anesthesia. In the case of the general anesthetics there is a loss of consciousness and therefore a reversible coagulation of some of the brain proteins; but this is merely a limitation of our present anesthetics and is not a theoretically necessary concomitant of anesthesia.

The biological people are always telling us that the reactions in the living organisms are not necessarily the same as those in the test tube. Theoretically they are wrong; but practically they are right

for the present. Consequently we knew that the biologists would insist on experiments with living organisms. Young vigorous cultures of baker's yeast were made in Laurent's medium with 1.5 per cent. dextrose. Subcultures were made every twenty-four hours, the third subculture being used in the experiments. The yeast cells were examined under the ultra-microscope and photographed. The culture was then treated with the narcotizing concentration of amyl alcohol, about 2 per cent., and again placed under the ultra-microscope. After about ten minutes the Brownian movements slow up perceptibly and a few minutes later one can see a distinct flocculation inside the cells. Similar results were obtained with chloroform, ether, chloral hydrate, and paralydehyde. The narcotized culture was centrifuged, the supernatant liquid poured off from the cells, and fresh, sterile medium added. The cells were washed twice in this way and examined under the ultra-microscope. The material in the cells soon develops a slight Brownian movement, then the aggregates break up into smaller particles and the motion becomes more pronounced. At the end of twenty-five or thirty minutes, the material is peptized completely and the yeast cells are normal in every respect. The yeast cell will ferment the medium and will reproduce just like cells which have not had this abnormal treatment. If too much narcotic is added or if it is allowed to act for too long a time, the coagulation becomes more marked and cannot be reversed. The cell is dead.

In the summer of 1930 I had occasion to tell some of the people at Woods Hole about our work. They have all studied marine eggs and they promptly cited these to show that we were wrong. When one administers an anesthetic to marine eggs (I have forgotten the kind), there is no change that can be detected by the eye and the contents of the eggs become less viscous. Further administration of the anesthetic leads simultaneously to visible coagulation, increased viscosity, and death. They interpreted the phenomena as meaning that a small amount of anesthetic peptized the contents of the egg and anesthetized the egg, while a larger amount coagulated the contents of the egg and caused death. They claimed that anesthesia was reversible peptization of something and not reversible coagulation of proteins. The failure to get visible changes during anesthesia was admitted by both sides to be unimportant, as the experimental error would be large if the hypothetically coagulated material differed but slightly in index of refraction from the medium. The important

point was the decrease in viscosity as measured, which the biologists said connoted peptization.

Fortunately, there is a perfectly satisfactory answer to this, which we had formulated before the objection was raised. When a ceric oxide sol is precipitated by the beta rays of radium, there is a decrease in viscosity followed by an increase, just as with the marine eggs. This is not a question of a preliminary peptization, because the increase in viscosity and the visible coagulation go on even if the beta rays are cut off. There is therefore nothing in the behavior of marine eggs to justify the assumption that a small amount of anesthetic peptizes the contents of the egg and that a larger amount coagulates them. As a matter of fact similar results have been obtained by exposing marine eggs to radium.

The real test of a theory is its ability to account for new phenomena and I propose to show that the theory of reversible coagulation of proteins is capable of coordinating all sorts of phenomena. We are making the additional explicit assumption that there is increased irritability as the nerve proteins approach the point of instability and the beginning of reversible coagulation. One would normally expect with increasing amounts of anesthetic to observe irritability, anesthesia, and death in case the coagulation becomes irreversible. It is well known that there is a period of irritability before anesthesia begins and after it passes off. In fact, our additional hypothesis was put in specifically to cover this and must justify itself independently. Since strychnine has a stimulating effect in small doses and causes death when administered in larger amounts, it seemed probable that there might be a range of concentrations perhaps very narrow, within which strychnine might act as an anesthetic. This was not very good reasoning, because strychnine kills usually with tetanic convulsions and also interferes with the oxygen metabolism. In spite of this, the prediction in regard to strychnine was verified. It is a simple matter to anesthetize a frog with strychnine because he can breathe through the skin. The frog will stay in a deep narcosis for several days. It is also possible to anesthetize a dog with strychnine provided he is given oxygen to minimize the unwanted action of the drug.

Professor Otto Rahn of the College of Agriculture reported at a meeting of the Research Club on the action of mercuric chloride on bacteria. If the corrosive sublimate was administered in small

doses or for short times, there was no apparent deleterious action. If larger doses were given or if a small dose was allowed to act for a longer time, a range of dormancy was observed. The bacteria could be aroused from dormancy by elimination of the mercuric chloride. If the doses were still larger, the bacteria died. Since the test for the state of the bacteria was the rate of increase of the colonies, the analogy with the ordinary anesthetics made us predict that small doses should give a greater rate of increase of the colonies than the normal and this actually occurred.

Dr. M. J. Brown of the Roessler and Hasslacher Chemical Company called my attention to the effect of hydrocyanic acid on the eggs of some scale insect found on citrus trees. A relatively high concentration of hydrocyanic acid killed the eggs of the scale; but a low concentration stimulated the eggs so much that a larger percentage hatched than in the control groups. These are merely a few instances out of an enormous number that could be given of the law accepted universally by biologists, physiologists, and bacteriologists that all depressor substances exert a stimulating effect when used at an appropriate dilution. Nobody has connected it before with the reversible coagulation of proteins, so this scores one for Claude Bernard.

By measuring the chronaxie we can get an independent answer to the question whether irritability of nerves is due to a reversible coagulation of the proteins or to a dissolving in the lipoids. I am not going to bother you with telling you just what is meant by chronaxie, though I really do know. For our purposes it is enough that chronaxie has to do with a response to electrical stimuli and that it is smallest when the nerve is most sensitive. It is one of these back-handed things, like pH, which gets larger as the solution becomes less acid.

Lapicque has shown, and Richter at Cornell has confirmed the fact, that with varying acidity the maximum chronaxie comes at about the isoelectric point of the proteins. When there are two proteins with widely differing isoelectric points, as in the frog, there are two maxima, one at or near each isoelectric point. This should not be the case if the phenomenon were due to lipoids. If isoelectric points exist at all for lipoids, they are not of sufficient importance to be recorded in the literature and are certainly not characteristic. We may therefore consider it as proved that irritability of a nerve or a muscle is dependent primarily on the state of the colloids.

Nobody has yet had the audacity to claim that irritability is a function of the proteins and anesthesia a function of the lipoids. That would be tantamount to saying that it was purely a coincidence that the biologists, physiologists, and bacteriologists found that all depressor substances exert a stimulating effect when used at an appropriate dilution.

In terms of Claude Bernard's theory a local anesthetic must be a substance which is taken up sufficiently rapidly and completely by the proteins in the immediate neighborhood so that it is not transported through the whole system by the blood. Administering adrenaline along with novocaine closes the capillaries to some extent and thereby helps localize the action of the latter. Claude Bernard did not discuss this because local anesthetics were not known at that time.

Claude Bernard did explain the joint action of morphine and ether or chloroform. Morphine, ether, and chloroform apparently act on the brain before they act on the sensory nerves, as is shown by the fact that the patient becomes unconscious before he loses the sensation of pain. Morphine acts less rapidly on the sensory nerves than do the true anesthetics. Consequently the administration of morphine will displace ether or chloroform from the brain to the sensory nerves and will cause anesthesia with less ether or chloroform than would be needed without the morphine. The first distinction between an anesthetic and a narcotic is that anesthetics act first on the sensory nerves and then on the brain, while narcotics act first on the brain and only considerably later on the sensory nerves.

So far as the general public is concerned, the chief difference between an anesthetic and a narcotic is that a narcotic is a habit-forming drug. In terms of Claude Bernard's theory, the difference between a habit-forming drug like morphine or cocaine and an anesthetic like ether or chloroform must be that the ether is eliminated relatively rapidly, while the morphine or some of its reaction products are retained. Experimentally, this has been found to be true. A corollary is that a compound which would peptize the colloids of the sensory nerves and which had no deleterious effect on other parts of the organism should furnish relief to drug addicts. We believe that sodium thiocyanate will do this; but we have not yet been able to get a doctor who had such patients to try it.

Claude Bernard tried one very interesting experiment on a dog which should be repeated. He gave a dog for four days running a dose of morphine which produced unconsciousness the first day. On the fourth day the dog had acquired such a tolerance to morphine that it did not go to sleep. Claude Bernard gave the dog a violent purgative and found that the dog was then as good as new with regard to its tolerance to morphine. If the facts are as stated, there seem to be two possible explanations. The purgative may have swept out the substance causing tolerance or it may have swept out everything else and left the liver free to eliminate the substance in its own way. On the other hand, the dog became very constipated and we know now that a great deal of the morphine administered passes out in the feces. It may be that there was no real tolerance and that the dog did not go to sleep because of irritation produced by the constipation.

Nitrous oxide (laughing gas) does not coagulate yeast and does not anesthetize it. Nitrous oxide does not coagulate albumin and yet it is an anesthetic for man, being much used in dentistry. It apparently interferes with the oxygen metabolism, giving rise to acid products which cause the flocculation. Wieland, whose critical study on nitrous oxide led to the discovery of acetylene as an anesthetic, was the first to emphasize the necessity of separating nitrous oxide and acetylene from the narcotics of the ether and chloroform type. He points out that these gases produce an effect similar to mountain sickness. He is led to the view that there is an inhibition of oxidation especially in the brain.

There are a number of problems to be worked out. Histamine apparently kills by action on the sympathetic nerves. The site of the action of strychnine appears to be certain of the synapses in the spinal cord. Resistance to impulses going through the synapses is decreased and inhibition is removed or cut down. The result is that an impulse going through a synapse has an uncontrolled spread and tetanic convulsions result. Curare acts on the motor nerves and potassium salts on the motor muscles. In terms of Claude Bernard's theory this should mean that there are different proteins in the different parts of the body, which is probable, and that they show selective adsorption for these drugs. As we do not know what these proteins are or what their properties are, we cannot tell whether this

is or is not the right explanation. It makes a first-class working hypothesis, however.

There are a lot of very curious things to be explained. Hedgehogs are affected very slightly by morphine. Morphine sets a cat nearly crazy. This probably is a question of degree and not of kind, the cat being brought into the irritable stage, which is usually not especially noticeable. I know one man whose reactions to morphine are like those of a cat. Though caffeine is an agglomerating agent, it only produces sleep when administered in very large amounts. Its chief property seems to be to produce mild irritation of the sensory nerves, which then keep the coffee drinker awake. Here there are no end of variations. One man is very susceptible to coffee and another is not. The same man may not be susceptible to coffee at one age and may be when he grows older. This is undoubtedly connected with changes in the sensory nerves; but the correlation has not yet been shown. The range between sleep and death with alcohol is fairly large in the case of man if he does not drink too rapidly. With goldfish the two points are practically identical. On the other hand, we have been unable to put a rabbit to sleep with alcohol.

There is one very interesting case to which we know the answer. Birds are apparently nearly immune to strychnine. It is possible to use poisoned grain which will kill small mammals without any danger to grouse, quail and pheasants. One did not like to assume a special set of proteins in birds, because the response to other drugs is fairly similar in birds and mammals. It seemed more likely that there was some special thing about strychnine and this proved to be true. If one injects strychnine into a bird, it dies. What happens is that with many birds strychnine does not pass into the blood. It is like the case of snake venom with man. The poison can be swallowed with impunity but kills if it gets into the blood.

At Woods Hole they challenged me to take up the case of strychnine. The tetanic convulsions due to strychnine can be checked by chloroform (an anesthetic), by sodium thiocyanate (a peptizing agent), by ephedrine (at that time unclassified), by curare (which acts on the motor nerves), and by potassium salts (muscular poison). It was claimed that the theory of Claude Bernard could not be made to cover all these cases unless it was made so general as to be valueless. Any stone is good enough to throw at a dog and they overlooked the fact that the same objection would apparently apply to any ex-

planation. To be logical they should have denied the accuracy of the alleged facts; but then there would have been nothing to explain.

I accepted the challenge. As has been stated, strychnine appears to act on certain of the synapses in the spinal cord, decreasing or removing the inhibition. Any irritation of the sensory nerves is liable to produce tetanic convulsions. Strychnine nitrate is an agglomerating agent coagulating a 2 per cent. albumin sol. Application of strychnine nitrate to the dorsal root ganglia causes agglomeration, as was shown by special experiments on swelling and shrinkage.

Chloroform anesthetizes the sensory nerves, thereby preventing external impulses from reaching the spinal cord. Curare changes the chronaxie of the motor nerves, thereby blocking impulses from the spinal cord so that they do not reach the muscles. Potassium salts paralyze the muscles and they cannot then respond to the impulses received. Sodium thiocyanate probably displaces the strychnine in the synapses, peptizing the proteins there. It will also peptize the sensory nerves so that they are much less irritable. With the sodium halides this latter is the main effect and the displacement of the strychnine is probably negligible. Ephedrine turns out to be a peptizing agent and therefore belongs with sodium thiocyanate.

It is much like a telephone system. You will not ring the subscriber's bell if he has left the receiver off the hook, if there is a break in the telephone wire inside or outside the house, or if the telephone company's power plant goes out of commission. We had hoped to have chloroform break the wire in the brain; but it does not do it. Decerebration or decapitation does not prevent the tetanic convulsions due to strychnine; but cutting all of the sensory nerves to the spinal cord does. Tying off the blood supply to the leg does not prevent tetanic convulsions in the leg; but cutting off the sensory nerves to the leg does.

Another thing that looked like a bad hurdle is that ordinary sleep is obviously due to a reversible coagulation of some portion of the brain and yet potassium bromide, a peptizing agent, is given as a cure for wakefulness. The bromide does not put one to sleep. It peptizes the sensory nerves, making them less irritable. It is consequently easier to go to sleep. Nobody would call darkening the room or turning off the radio a hypnotic; but both those things make it easier to go to sleep.

Physicians always give potassium bromide as a sedative, so far as I know, instead of sodium bromide, and it is quite depressing to see how in other cases they use potassium and sodium salts interchangeably. Since potassium salts are roughly two to ten times as toxic as the corresponding sodium salts, no physician should give a potassium salt when he can prescribe a sodium salt. There is not much danger of potassium poisoning in most cases, though it has happened at times; but the potassium ion will counteract the effect of the acid radical more than the sodium ion will and is consequently objectionable. Many physicians believe that there is no effect until one gets up to the toxic dose; but that is absurd. The prevailing use of potassium salts is due to two things: German propaganda and the fact that some sodium salts, the nitrate for instance, are more deliquescent than the potassium salts.

When one disinfects with hypochlorites, it is probable that there is direct chemical action; but this is not true in a great many cases. We are often dealing with a reversible or an irreversible coagulation of bacteria. From this point of view antisepsis corresponds to anesthesia and disinfection to death of bacteria. It is interesting to note how people have seemed to prove the occurrence of a chemical reaction by the simple process of not mentioning the experiments that disprove the concept.

Let us assume a mass-law reaction between bacteria and disinfectant:

$$\text{bacteria} + \text{disinfectant} \rightarrow \text{dead bacteria.}$$

It is common knowledge that increasing the concentration of the disinfectant will increase the rate of disinfection and the number of dead bacteria, at least until all the bacteria are dead. This is in qualitative agreement with the mass law. If larger amounts of live bacteria are taken, there should also be an increase in the rate of disinfection, because we have increased the value of the other term. Experiments with constant amounts of disinfectant and increasing amounts of bacteria do not go at all as they should on the assumption of a chemical reaction. Increasing the mass of the bacteria decreases the effect of the disinfectant very much. McClintic found that when the bacterial mass was increased five-fold, the phenol coefficient of disinfectant "B" dropped from 15.6 to 11.6. If the number of bacteria in any experiment be made very great, there will be no deaths due to the disinfectant. This is an impossible situation if we are

dealing with a chemical reaction, but it can be predicted from the theory of Claude Bernard. If the number of bacteria is so large that the amount of disinfectant adsorbed per bacterium is less than that necessary to coagulate it irreversibly, there will be no deaths.

There is another experiment which seems to be in favor of a theory of chemical reaction until one examines it critically. If dead bacteria be added to the disinfection experiment, the effect of the disinfectant should be decreased if the reaction is reversible. Lange did this experiment and found that the effect of the disinfectant was decreased. The difficulty with this is that the reaction is not reversible. Adding dead bacteria to any system cannot bring any of them to life, no matter how many one adds. What happened was that the dead bacteria adsorbed enough disinfectant to lower its concentration and consequently its rate of disinfection.

With disturbances of health due to reversible coagulation of proteins, anything which will peptize the coagulated proteins will tend to restore health. The order of peptization of many proteins by salts is given by what is known as Hofmeister's series: thiocyanates, iodides, bromides, chlorides, sulfates, the thiocyanates peptizing the proteins the most readily and the sulfates the least readily.

Mention has already been made of the use of bromides as an indirect method of causing sleep and of the probable success in using sodium thiocyanate to relieve drug addicts. We have shown that with rabbits sodium thiocyanate counteracts the effects of ether, amytal, morphine, strychnine, and anaphylactic shock to some extent, which is as it should be. Clowes has obtained similar, perhaps better, results with ephedrine, which is also as it should be, because ephedrine peptizes albumin more readily than does sodium thiocyanate. With human beings sodium thiocyanate and ephedrine counteract the skin reactions with histamine and with hay fever extract. Sodium thiocyanate counteracts distinctly the effect of alcohol on man.

Since hay fever seems to be of the same general nature as anaphylaxis, and since ephedrine gives temporary relief, it seemed probable that sodium thiocyanate would act similarly. In September, 1930, a friend of the family told me that she was suffering so much from hay fever that she would try anything, even something that I recommended. I made up a 1 per cent. solution and suggested that she spray with that. I heard nothing from her for three days and then I could not stand it any longer. Over the telephone I was told

that she had not had a bit of hay fever since I gave her the bottle. That was good news, almost too good, because we do not live in an age of miracles. What had happened was that the weather had turned cool that evening and the hay fever had of course disappeared without my medicine ever being tried. I have often thought since what a reputation I would have got in Ithaca if I had taken that bottle down twenty-four hours earlier.

The sensitive plant closes its leaves when touched. That should mean that its proteins are very close to the isoelectric point, so that it is biologically similar to the cat with morphine. We don't know what the proteins are in the sensitive plant or what their isoelectric points are. Claude Bernard has stated that "the action of anesthetics is very general. They react not only with animals but also with plants. Thus they stop the movements caused in sensitive plants by external stimuli, the movements of the anthers of some flowers for instance." Bose has found that plants anesthetized with ether go through a preliminary period of increased irritability or stimulation. A dilute alcohol acted as a stimulant, whereas a concentrated alcohol solution acted as a depressant. It was therefore practically certain that a suitable treatment with a sodium thiocyanate solution would soothe the nerves of *Mimosa pudica,* or whatever substitutes for nerves plants have, to such an extent that the plant will be relatively insensitive to external stimuli.

Professor Knudsen of the College of Agriculture was good enough to grow a number of sensitive plants for us and to help us with the experiments. When one of the plants is sprayed with a 5 per cent. solution of sodium thiocyanate and when the roots are later watered with the same solution, it becomes relatively insensitive to mechanical stimulation. Even comparatively powerful blows elicited only a faint folding response on the part of the leaves and the eptioles dropped only slightly.

The most recent development of the theory of Claude Bernard is the colloid chemistry of insanity. Abnormal thinking, if persisted in, will be classed as insanity. We can get the brain into an abnormal state either by getting it over-coagulated or by getting it over-peptized. There must therefore be two types of insanity which have not hitherto been differentiated properly by medical men. In one of the types the mental disorder may be classed as coagulation insanity or Insanity C, and in the other as dispersion insanity, or In-

sanity D. Dr. Lang of the Willard State Hospital prefers to use the term cycloid type instead of coagulation insanity and schizoid type instead of dispersion insanity. As his terms tie in better with present medical usage, I hope that they will be adopted. I could not have suggested them because I did not know what they meant until he told me, or even which was which.

The cycloid insanity or coagulation insanity should be alleviated by sodium thiocyanate and should be made worse by sodium amytal, a coagulating agent. The schizoid insanity or dispersion insanity should be made worse by sodium thiocyanate and should be alleviated by sodium amytal. This means that we have a direct chemical test for classifying cases of insanity as over-coagulation or over-dispersion and that we are thereby freed from the very real danger of grouping together different types of insanity because the outward symptoms happen to be similar. A boy may be doubled up with pain because he has a cramp in the thigh or because he has eaten green apples; but the remedy should not be the same in the two cases, though both are cramps.

While it is possible that somebody could have evolved the concept of the colloid chemistry of insanity from his inner consciousness, nobody did. The data for it were present in the literature but meant nothing to anybody until they were viewed with reference to the theory of Claude Bernard.

Borg gave 2-10 grains of sodium or potassium thiocyanate (it should have been only sodium thiocyanate) three times a day for one to four weeks to a group of patients suffering from high blood pressure. Toxic psychoses developed in four patients with disorientation, hallucinations of sight and hearing, mania, confusion, and ideas of persecution, singly or in combination. They lasted only from five to seven days after the drug was discontinued. This is evidently production of dispersion or schizoid insanity.

Hysteria often goes over into insanity and this must be due to a coagulation of the brain colloids. Shipwrecked sailors often get hallucinations and become insane before jumping overboard or before drinking salt water. Alcohol is credited with nearly 10 per cent. of the mental disorders that lead to hospital incarceration. Since alcohol is a coagulating agent, these cases must be of the cycloid type.

There are two phases in the action of salts of lead on the brain. In low concentrations or in the initial stage of poisoning, stimulation

of the brain and of the optic nerves causes hallucinations of sight and mental disturbances which resemble those of delirium tremens. The second phase is exactly what one would expect from a coagulating agent. The stage of stimulation passes into depression, during which the early symptoms of paresis appear. In more advanced stages there is actual paralysis and damage to the nervous tissue. Dr. Kehoe has supplemented this by pointing out that lead tetraethyl is soluble in lipoids. It can and does get into the brain and produce insanity, whereas white lead, which is not soluble in lipoids, does not get into the brain ordinarily and produces the usual form of lead poisoning.

In 1926 Wright obtained remarkable results with some insane patients by administering 100-300 grains of sodium bromide per day. One patient was so violent that she bit off parts of three ears. After treatment with sodium bromide she became industrious and helped with the ward work. A nurse stated: "Before the treatment was begun it took four or five of us to bathe and dress these patients. Yesterday morning (*i. e.,* some months after treatment was instituted) I supervised the bathing and dressing of these patients alone."

About 25 per cent. of the patients who received the treatment were classed as unimproved. Wright does not distinguish two types of insanity and consequently we cannot tell whether the failures were due to treating the wrong type of patient or to some other cause. Wright does state, however, that most of the failures have occurred in states of apathy. These would be expected to be dispersion or schizoid insanity and should not be helped by bromide. The work which Dr. Lang is now doing shows that this guess was right. In some experiments in which a great deal of sodium bromide was given, Wright apparently carried some patients clean over from cycloid to schizoid insanity. This has since been done intentionally by Dr. Lang.

The reverse case in which patients with schizoid or dispersion insanity are benefited by treatment with a coagulating agent has been studied at the University of Wisconsin, though they did not, of course, speak of dispersion insanity or of a coagulating agent. Loevenhart, Lorenz, Martin and Malone have studied the effect of carbon dioxide, a coagulating agent, with very striking results. "The most favorable and striking reaction occurred in those patients who had been mute and mentally inaccessible for long periods of time. In

these cases, after a short period of respiratory stimulation, this inaccessibility disappeared and the catatonia passed off. A number of patients have carried on conversation."

This work was published in 1929. In March, 1931, Dr. Karl Langenstrass of St. Elizabeth's Hospital in Washington, D. C., reported at the annual clinical session of the American College of Physicians in Baltimore, that he had been treating cases of catatonic stupor with a mixture of 25 per cent. carbon dioxide and 75 per cent. oxygen, supplemented by suggestion therapy, a mild hypnosis, as soon as the gas mask was removed after the patient had inhaled the mixture for about half an hour. Typhoid vaccine and coli fluid were also administered for the purpose of producing a rise in temperature. One patient who had been in a mental stupor for over ten years has now been perfectly normal for two years. One woman is now supporting a drunken husband and three or four children. In all, three cases have been sent out into the world again functioning normally without any need of further treatment. The original treatment lasted about a month.

In 1930 Lorenz treated cases of catatonic stupor with sodium amytal, an anesthetic. Of one he says that, on coming out of the narcosis, "she responded to conversation and asked for food and drink. She continued in this aroused mental state for a period of four hours, when no further efforts were made to keep her awake and she dropped into what appeared to be a natural sleep for a period of five hours, when the mutism, muscular rigidity, and active negativism slowly redeveloped."

Ten years ago Berger injected small amounts of cocaine hydrochloride into eleven patients suffering from catatonic stupor and noted that the majority became active immediately after the first injections. The improvement did not last more than an hour or two. It is not clear why the effect of the cocaine was not primarily local.

There seems to be no question but that catatonic stupor is a case of dispersion or schizoid insanity and that epilepsy and manic depressive insanity are cases of coagulation or cycloid insanity. Paresis produced by lead poisoning is also unquestionably cycloid insanity. We cannot go much beyond that at present; but it is very probable that we shall find that some of the classes now recognized by medical men are not sufficient.

I have tried to show you that an application of the theory of Claude Bernard, of reversible coagulation of proteins helps us in the study of phenomena connected with anesthesia, drug addiction, disinfection, strychnine, histamine, potassium salts, curare, hay fever, and insanity. It will probably help us in getting a better understanding of anaphylaxis and of immunity reactions. That is quite a showing for two years' work by three men. It is due entirely to the enthusiasm and efforts of Dr. Richter and Mr. Rutzler that so much has been accomplished. The work on insanity is really the outgrowth of work started by Dr. S. DeW. Ludlum of Philadelphia, though the development has been along superficially different lines. Without Dr. Ludlum there would have been no colloid theory of insanity today.

Since it is now possible, at least in some cases, to change a man with one type of insanity temporarily to normal, to the other type of insanity, and back again, it should be possible to develop a psychology of insanity which would be really worth while.

MEDICAL AND PHARMACEUTICAL NOTES

NEW CHEMICAL ELEMENT 87 REVEALED BY X-RAYS—The discovery of element 87, one of the two remaining missing or "doubtful" members of the chemist's periodic table, is reported in the mineral "samarskite," by Prof. Jacob Papish and Eugene Wainer of the department of chemistry of Cornell University here, who used X-rays to examine it.

A discovery of element 87, one of the ninety-two ultimate building blocks of the material world, was announced a year ago in the minerals "lepidolite" and "pollucite" by Prof. Fred Allison and Dr. Edgar J. Murphy, of the Alabama Polytechnic Institute. The Cornell researchers doubt this claim. They have examined solutions reported by Professor Allison to contain number 87 but decided that it is present, if at all, in extremely small quantity.

Professor Allison used a novel method of examination devised by himself, called the "magneto-optic" method. The reliability of this has not yet been tested by other investigators. The X-ray spectrum used by Professor Papish and Mr. Wainer, on the other hand, is widely known to scientists and was successfully used in 1926 at the University of Illinois to identify America's first element illinium, number 61, for the first time. In the hands of competent investigators it is a powerful way of detecting an element.

Professor Papish and Mr. Wainer decided to examine the very complex mineral "samarskite," by means of the X-ray spectrograph. "Samarskite" is a curious department-store kind of a mineral containing uranium, tantalum, cerium, columbium and smaller amounts of many other elements.

The Cornell chemists can base their claim to priority in this discovery, if they are successful, on the additional fact that they chemically concentrated the preparation in which they claim to have found this elusive element. This was not done by Professor Allison.

A large quantity of the mineral was heated in a stream of hydrogen chloride gas and a mixture of chlorides of metals driven off. The distillate, after conversion into sulphates, was purified by various chemical processes and finally fractionally crystallized as the alum salts of the mixture of the alkali metals.

The least soluble alum obtained, which was rich in the alkali metal caesium, the nearest family relative of 87, was then subjected to tests in the X-ray spectrograph. Five lines agreeing perfectly with those to be expected from the missing number 87 were found on the photograph. The basis of this test is that each chemical element gives characteristic lines, on the X-ray spectrogram, whose position enables the physicist to tell its atomic number, or place in the series of elements.

The authors believe that they have established the presence of the missing element in samarskite. However, they state:

"A name for the element will not be announced until additional confirmatory data are obtained."

Number 87 has been called "eka-caesium" because of its close relationship to caesium. It is the next door neighbor to radium in the periodic classification and should be similar in properties to sodium and potassium, the so-called alkali metals. The behavior of the Cornell samarskite extract agrees with this requirement.

The further concentration of the mixture in which number 87 has been found will be watched with great interest by the scientific world. Several previous claims of the discovery of 87 have been disproved by later experiments. The properties of the element should be of great interest. The discovery of chemical element 87 was predicted just sixty years ago by Mendeleeff, the Russian chemist, who first discovered the periodic relationship between the elements which make up our universe.

Basing his prophecies on the behavior of the elements known in 1871, Mendeleeff described the elements of series 10 of his periodic table, although all of them were at that time unknown except uranium and thorium. A special translation of Mendeleeff's original paper is quoted herewith:

"Then in the 10th series we might expect basic elements belonging to groups I, II and III. They must have atomic weights of about 210 to 230."

Of these, the one predicted for group II is the now famous radium, whose atomic weight is 226, and the one in group III is actinium, another radio-active element. The one belonging to group I is the new element 87. Mendeleeff stated further:

"The first will be similar to caesium, the second to barium, and all their oxides will have the character of strong bases, because in

this series even thorium in its oxide has distinctly basic properties, and even uranium of the same series in its oxide still has a clearly basic character."

This means that the new element 87 will combine with water to form a strong lye, probably the most caustic substance possible. In addition to the properties which Mendeleeff was able to predict for element 87, it is now known that it is probably radio-active like radium and the other elements of its series. The property of radio-activity has been discovered since Mendeleeff's time, but merely adds another confirmation to his statement of the relationships which he found governing the ninety-two chemical elements.—*Science Service.*

Digestive Ferments in Post-operative Treatment—Successful experiments in the use of digestive ferments to treat troublesome adhesions which may form after abdominal operations were reported to the American College of Surgeons by Dr. Alton Ochsner and Dr. Earl Garside, of Tulane University of Louisiana School of Medicine, New Orleans.

Such adhesions are usually of great value to the surgeon for a time, but after they have served their period of usefulness they become a menace to the patient, Dr. Ochsner explained. Certain individuals have a tendency to formation of fibrous adhesions and in such people operative treatment does little good, as the adhesions usually reform.

Drs. Ochsner and Garside studied 280 animals and found that in every animal adhesions reformed after operation to divide the pre-existing ones. They then tried introducing various solutions into the abdominal cavity after operating on the adhesions. With a solution of the digestive ferment, papain, few or no adhesions reformed in over nine-tenths of the cases. Papain is obtained from the juice of the fruit of the papaya. Another ferment, trypsin, prevented the reformation of adhesions in nearly half the cases. The theory is that after the adhesions have been divided, the ferments act to assist in removing the excessive amounts of fibrinous adhesions before the organization of the fibrous tissue into new adhesions has occurred.

Dr. Ochsner said that the digestive solutions have been used on fourteen patients, but it is still too soon to draw any conclusions as to the result.—*Science Service.*

NEW USES OF OXYGEN FOR TREATING DISEASES—A number of new developments in the use of oxygen for treating diseases were brought out at a special session devoted to the subject at the Congress of Anesthetists. Taking part in the discussion were Dr. John J. Wittmer, medical director of the New York Edison System; Dr. John H. Evans, chairman of the board of governors of the International Anesthesia Research Society; Dr. Clarence J. Durshordwe, of Buffalo; and Dr. Alvin Barach, of Columbia College of Physicians and Surgeons and Presbyterian Hospital, New York.

In tuberculosis oxygen is useful for promoting the growth of healthy tissue. It has the same effect in large burns which cannot be successfully treated in any other way. Diabetes, pneumonia, certain types of kidney and heart disease, and asthma and hay fever, are benefited by oxygen treatments, the discussion showed. A case was reported in which the patient had a very severe degree of heart trouble with dropsy. Every known remedy was used unsuccessfully. Finally the patient was put in an oxygen chamber which produced the first beneficial effect, after which the ordinary remedies for heart disease were used effectively.

FLUORINE AND MOTTLED TEETH—Dogs with mottled teeth, an endemic condition of the enamel produced by the presence of fluorine in drinking water, have been achieved experimentally by Dr. Margaret Cammack Smith, of the Home Economics Department at the University of Arizona.

Six months ago Dr. Smith completed her experiments with the drinking water at St. David, Arizona, and determined that fluorine in the drinking water at that place was responsible for the existence of mottled teeth.

At first the mottled condition was only produced experimentally in white rats, but now for the first time this condition has been given to the larger animals. The mottled condition has been produced after a six-months' feeding experiment.—*Science Service.*

FIND SKIN HAS NO DISINFECTING POWER—The skin does not have the power of disinfecting itself or of killing microbes that get

on it, John F. Norton and Marguerite F. Novy, of the Detroit Department of Health, reported to the recent meeting of the American Public Health Association.

One group of scientists, Dr. Lloyd L. Arnold and associates of the Illinois State Department of Health, have reported experiments showing that the skin did have this disinfecting power. The Detroit investigators were unable to find any evidence of inherent germ-killing properties of the skin. Microbes that had been left on the skin for about ten minutes did lose their ability to live, but if the skin was kept moist, only a few of them died. Apparently it was the drying effect of being left on the skin that killed the germs, and not the skin itself. Filter paper, glass slides, tanned hides and other materials produced the same effect as the dry skin.

Two common disinfectants, mercurochrome and gentian violet, may be good germ killers, but they interfere with the body's own mechanism for killing germs, it appeared from studies reported at the same session by Emerson Megrail and D. J. Shaw, of Western Reserve University. Solutions as weak as 0.1 per cent. mercurochrome and 0.2 per cent. gentian violet apparently repelled the leucocytes, scavenger cells of the body, and kept them from the site of infection which they ordinarily would try to clean up.—*Science Service.*

THE DIFFERENTIAL ANALYSIS OF STARCHES, James B. McNair, Field Museum, Chicago, Botanical Series, Volume IX: 1-44, 1930. Eleven processes of analysis furnish data by which starches may be differentiated. These processes are: (1) histological microscopic examination to determine the form and size of the grains, position and character of the hila, characteristics of the lamellae, orientation, etc.; (2) the degree of polarization; (3) the iodine reaction; (4) the gentian violet reaction; (5) the safranin reaction; (6) the temperature of gelatinization; (7) the chloral hydrate-iodine reaction; (8) the chromic acid reaction; (9) the pyrogallic acid reaction; (10) the ferric chloride reaction; and (11) the Purdy solution reaction. These tests are carried out on small amounts of material by the aid of the microscope and require individually not more than one hour's time. By these tests it is possible to tell the difference between starches of different plant families, as corn starch from

potato starch; between the starches of the members of one family of plants as wheat, rye and barley; or from different varieties of one species, *e. g.*, the starch of ginger root from Jamaica and the ginger root from Cochin China, or between the starches of pod corn, pop corn, flint corn, dent corn, soft corn, sweet corn and starchy sweet corn.

Liver Enzyme Makes Vitamin A From Carotene—An enzyme has been found in liver which transforms carotene, the yellow coloring matter of carrots, into vitamin A, Harold S. Olcott and Duane C. McCann, of the State University of Iowa, have just discovered.

The fact that carotene, which is found in other vegetables besides carrots, was changed to vitamin A in the body has been known to scientists for some time. The transformation has never before been performed outside the body, however.

Preliminary experiments showed that carotene was destroyed and vitamin A appeared when carotene was kept in a warm place for a time with fresh liver tissue from the bodies of rats that had lacked vitamin A. It was supposed that the reaction was due to an enzyme.

Further research, using a liver extract instead of fresh liver, proved this to be the case, the Iowa investigators report. They suggested that the new enzyme should be called carotenase.—*Science Service.*

French Tincture of Iodine (Liquor Iodi Simplex)—The report of the Pharmacy Sub-Committee to the Pharmacopœia Commission, August, 1930, states that a new preparation of iodine is required, corresponding to the so-called "French Tincture of Iodine," and that it should be a 10 per cent. w/v solution of iodine in 95 per cent. v/v alcohol. There are probably two important reasons why such a preparation is advocated. First, the recommendation of the International Conference that met in Brussels in September, 1902, that Tinctura Iodi should be a 10 per cent. solution of iodine in 95 per cent. alcohol; and, secondly, the demand from the medical profession for a solution for the exhibition of free iodine which does not contain any iodine in combination, such as the potassium iodide

in Tinctura Iodi Mitis and Tinctura Iodi Fortis. It is stated that solutions containing iodides are more liable to give rise to iodism than a solution containing iodine alone. Such a solution as that given above is unstable, as some of the iodine enters into combination, and similar solutions which have been official in the foreign pharmacopœias have been deleted for this reason.

It has been shown that hydriodic acid, aldehyde and acetic acid are formed on keeping a simple solution of iodine in alcohol. There is reaction between the iodine and the alcohol, forming hydriodic acid and aldehyde, the latter then forming acetic acid, which in turn esterifies some of the alcohol. The loss of iodine from this cause is stated to be rapid for the first two months, but becoming less rapid afterwards, and reaching a state of equilibrium in about eight months. It has been found that the addition of potassium iodide prevents these changes. This has been confirmed by workers both in this country and on the continent, two of the latter showing that the loss of free iodine in six to twelve months was 20 per cent. of the total.

Experiments carried out by the author on a sample of the proposed "French Tincture of Iodine" prepared under pharmacy conditions showed that during three months there was a loss of about 15 per cent. of free iodine, and a laboratory sample prepared with the purest resublimed iodine lost 13 per cent. of free iodine in two months. Other experiments in which heat was applied to hasten solution and others in which solution was made in the cold showed that as the iodine goes into solution it reacts with the alcohol, thus causing a loss of free iodine. The reaction continues for four months at least, the rate being slightly accelerated by light.

In view of the statements made by various workers, which are amply confirmed by the above experiments, it would appear that the Pharmacy Sub-Committee has erred by recommending that such an unstable preparation as a simple alcoholic solution of iodine be inserted in the British Pharmacopœia. The supposed advantage of having a solution free from combined iodine is defeated by the reaction of the iodine with the alcohol, forming the compound hydriodic acid, which also renders the solution strongly acid. Such a change does not take place in the tinctures which contain potassium iodide, and therefore they should meet all the requirements for alcoholic solutions of iodine.

A simple solution of iodine in alcohol loses free iodine by interaction, hydriodic acid being formed. This change does not take

place in the presence of potassium iodide. Foreign pharmacopœias have deleted simple alcoholic solutions of iodine, and have replaced them by solutions containing potassium iodide which are stable. The British Pharmacopœia should not accept a formula for a simple alcoholic solution. The requirements for solutions of iodine are met by the two solutions at present official.—J. P. Walmsley, *Pharm. J.*, July 25, 31.

NEWS ITEMS AND PERSONAL NOTES

Dr. Frederick W. Germuth, head of the Division of Research of the Department of Public Works, Bureau of Standards, Baltimore, and a frequent contributor to these pages, has been recently honored with the Decoration of the Double Wreath of the American International Academy for "distinguished researches and discoveries in chemistry."

The Prescriber, a monthly review of medical progress published in Edinburgh, celebrates its twenty-fifth birthday this month. The October number contains an Editorial article sketching the history of the journal. Started in a small way by the present Editor, Dr. Thomas Stephenson, this journal has steadily grown in size and influence, and today it has a world-wide circulation. A number of "birthday greetings" from old subscribers, and a plate showing views of the present offices at 13, Glencairn Crescent, Edinburgh, are features of the issue. The chief medical subject dealt with in this number is Skin Diseases, a review of which covers 31 pages.

"WELLCOME" PHOTOGRAPHIC DIARY 1932

The 1932 edition of the ever popular "Wellcome" Photographic Exposure Calculator, Handbook and Diary, is now available and, as usual, is replete with all the latest photographic information.

The past year has seen the introduction of many new films, the exposure and development factors of which will be found in the handbook. Following the usual custom the whole range has been revised and, when necessary, corrections made. These tables, which involve much labor in the testing of plates and films, place in the hands of photographers at a very low cost the results of expensive and laborious experimental work. An entirely new chapter on chlorobromide papers has been added.

In view of the increasing interest in cine work special attention has been paid to cine films, and the special table devoted to this type of work also refers to many films not previously included. Incidentally, it provides a comprehensive list of the most popular cine films.

This vade mecum of photography is an integral part of the outfit of the complete photographer. It places at hand essential information and data not elsewhere readily obtainable.

The "Wellcome" Photographic Exposure Calculator, Handbook and Diary is intended for pocket use; it is therefore always ready for instant reference. Memoranda pages are provided to enable personal records to be made of exposure, subjects, etc., on the spot, and the diary pages can be used for general records if desired.

Four editions are issued: Northern Hemisphere and Tropics; Southern Hemisphere and Tropics; Australasia and Tropics, and United States of America.

Price—75¢ copy, postage free.

"PLASKON," A NEW SYNTHETIC RESIN—According to a research report published by Mellon Institute of Industrial Research, Pittsburgh, Pa., a novel heat-reactive molding compound is now being produced commercially in the plant of Toledo Synthetic Products, Inc., Toledo, Ohio. This new urea-base compound, called "Plaskon," was evolved at Mellon Institute under a series of industrial fellowships sustained by the Toledo Scale Company. Copies of the report may be obtained by interested persons upon direct request to the institute.

"Plaskon" molding compound is said to be easily preformed, and it is pointed out that this property, in conjunction with the high speed of cure, makes possible rapid low-cost mass fabrication by the molder.

Fabricated "Plaskon" is described as unexcelled in color possibilities, combining bright colors with a hard, lustrous surface. Its base shade is one of neutral translucency, permitting pigmenting to give all colors of any intensity, either opaque or translucent. Obviously, as indicated in the publication, infinite variations in mottled or striated effects are possible.

The mechanical and electrical properties of "Plaskon" are said to be excellent.